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Policy Research Initiative
Projet de recherche sur les politiques

Genomics, Health and Society
Emerging Issues for Public Policy

Edited by
Bartha Maria Knoppers
Charles Scriver

Canada

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Foreword

Charles Scriver

The federal government's Policy Research Initiative partnered with a number of other agencies[1] to convene an international symposium in Toronto in June 2002. The following summarizes the origins and workings of that meeting.

Genomics is a new word (coined in 1987). It suggests a method of attack on problems in the genome. Genome is an older word (first used in 1920). It describes an aspect of genetics. It is an irregular Greek hybrid of the words "gene" and "chromosome." The word "genomics" attained its common currency as the era of the Human Genome Project unfolded.

Genetics is the branch of biology that deals with heredity and biological variation among related organisms. Genetic variation originates in mutation. This mutation, or change in molecular identity, occurs in a molecule of information known as DNA. The year 2003 is the 50th anniversary of the discovery of the chemical and physical structures of DNA, and what they signify for heredity.

Organisms such as *Homo sapiens* are the product, not only of their heredity but also of experience: the so-called dialogue between nature and nurture. Whereas our nature (heredity) is a manifestation of chance, namely how the genomes of our parents combined to become our own, the experiences we encounter during the progress of life are another expression of chance. Someone said that the organism is an expression of nurture acting in nature.

This conference addressed recognizable opportunities in genomic initiatives and ways to reconcile variation in genes and genomes with experience so unfavourable consequences (so-called "genetic disease") might be prevented or at least avoided in citizens, their families, and communities in Canadian society.

Why are the opportunities a matter for public policy? There are many answers and each in its own way would recognize that new knowledge has become available. Knowledge is a public good. There is basic knowledge about genes and genomes and the way they contribute to the health or "unhealth" of organisms. There is applied knowledge that can be used to create new products of commercial or medical significance. However, there are some important questions: Is the knowledge reliable? What are its benefits, or its hazards, when it is put to use? The poet had his way of inquiry: *Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?* (T.S. Eliot). One might add that there are various types of knowledge such as the unknown (scientific), the known (applied), the prohibited (censorship), and the "I don't want to know" (fear).

Canada has a system of universal health care. Almost 20 years ago, the Science Council of Canada anticipated the time would soon be at hand when the new knowledge of genetics, both human and medical, could be applied to health care, to benefit individuals, families, communities, and society. In 1991, the Science Council of Canada published Report No. 42 – *Genetics in Canadian Health Care*. The report addressed all the major themes that would be revisited in this conference over a decade later. Science Council Report No. 42 was prematurely born and its findings were little acted upon. But its time has come and the opportunities in genetics for health care, education, and commerce are now clearly recognizable, along with the hazards that may attend. In the meantime, the Science Council has been terminated but its Report No. 42 lives on at the following Web site <http://www.cgdn.ca/eng/news/publications/report42.html>.

The Policy Research Initiative and the Science Council of Canada are not the only ones to make excursions into genetics and its relevance to society in recent Canadian history. The Royal Society of Canada held a symposium in 1993, entitled Genetics and Society: What Society Expects of Geneticists (Scriver, 1993). Tensions between opportunities and potential hazards were discussed in that symposium. It was also recognized that science, being an assault on ignorance, results in knowledge about what was previously unknown and which could subsequently be applied. At the time, Canada was making its own low key investment in genomics, and it had an enviable record in applying knowledge about genetics to health care in many different regions of Canada.

In 1996, the Ontario Law Reform Commission, published its *Report on Genetic Testing*. It included chapters on genetic testing, human rights, property rights, paternity testing, insurance and employment testing, medical testing, and privacy and confidentiality. The Commission was disbanded that same year.

Isuma: Canadian Journal of Policy Research volume 2, no. 3, revisited Science Council Report No. 42 on genetics (Scriver, 2001) and reviewed its implications for health care, education, commerce, and ethics, acting, as it were, as a prelude to the present conference. As it happens, *Isuma* has been discontinued, leading one to ponder whether any open discussion of applied genetic knowledge confers a fatal illness to the concerned communities.

An exciting aspect of the Toronto symposium in 2002 was the enlargement of the "genetic" focus. The "partners" in this new symposium came from many sectors (academic, government, industrial, technology, law, medicine, economics, and ethics) to name only some. If genomic knowledge were still not seen as a public good, both global and regional, the reader would do well to consult a recent commentary in *The Lancet* (Thorsteinsdottir et al., 2003) where those contexts are given. Participants in the Toronto symposium wrote that article.

The following papers are adapted from the presentations at the conference. Not every speaker is represented, nor do these articles reflect all that the speakers might have contributed in subsequent discussion. Some of the articles reflect advances that have occurred since the meeting took place. The document is divided into five sections followed by a summary and conclusions. An appendix describes the contributors.

The major themes of the conference fell under five headings:

- setting the policy context;
- genetic medicine and privacy;
- intellectual property;
- implications for the developing world; and
- informing government.

In comparative terms, the conference dealt extensively with the ownership of genomic knowledge, less so with its use for personal and collective good (in health) and less still on the creation of new knowledge. They are mutually interdependent, but the balance reflects realities as addressed in the summary. In the meantime, the routes nations, such as Canada, will likely travel (if we seize the opportunities available in the so-called post-genome era) have been outlined by some of the major architects of the Human Genome Project (Collins et al., 2003) — and by others — as they consider both the future of biology (as it elucidates the states of health and disease) and the biology of the future (Rose, 2001).

If two thoughts encompass what emerged from the conference, they might be these. First, the opportunities for commerce, technology, and research move at a pace and in directions that no ordinary person can predict or anticipate. In this sector, there is danger that a public good of today may be sequestered as private property by tomorrow. The experience with the BRCA1 gene test is an example. Second, every human being is a genetic minority of one, because every person's genome is a unique entity. Accordingly, every disease that reflects a genetic cause or an inherited susceptibility is an "orphan disease." How does one provide health care (and protection of privacy) accordingly?

The implications for public policy in these two broad themes are awesome. What the corresponding policies might be are, to a considerable extent, found in the articles that follow.

Note

1 Canadian Biotechnology Advisory Committee, Canadian Institutes of Health Research, Genome Canada, Health Canada and Industry Canada.

References

Collins, F.S., E.C. Green, A.E. Guttmacher, and M.S. Guyer on behalf of the US National Human Genome Research Institute (2003) "A Vision for the Future of Genomics Research," *Nature*, 422: 835-847.

Ontario, Law Reform Commission (1996) *Report on Genetic Testing*, Ontario: Law Reform Commission.

Rose S. (2001) "The Biology of the Future and the Future of Biology," *Perspectives in Biology and Medicine*, 44: 473-484.

Science Council of Canada (1991) *Genetics in Canadian Health Care*, Report No. 42.

Scriver, C.R. (1993) "Genetics and Society: What Society Expects of Geneticists – Overview," *Trans Royal Soc of Canada*, Series VI, IV: 3-10.

— (2001) "Genetic Disease: An Orphan in Canadian Health Care," *Isuma*, 2(3): 113-118.

Thorsteinsdottir H., A.S. Daar, R.D. Smith, and P.A. Singer (2003) "Genetics – a Global Public Good?" *The Lancet*, 361: 891-892.

Part 1

Setting the Policy Context

Genomics, Health and Society

Claude Laberge

Introduction: The Human Genome

Over the past decade, the term "genomics" has become common parlance, heard every day by the public and used every day by the decision makers attempting to assess the probable consequences of this scientific discipline on health care. Genomics refers to the analysis of the genomes of living organisms, both anatomically (sequences and organization) and physiologically (expression and regulation). Genomes are made up of DNA, except those of certain viruses with RNA genomes that rely on cellular machinery to reproduce themselves.

The human genome comprises a ribbon of 3.2 billion nucleic acids (ATGCs) consisting of 30,000 to 35,000 genes distributed heterogeneously into islands rich in expressible sequences and deserts with few genes. These 30,000 to 35,000 genes code for approximately 150,000 to 200,000 proteins. These proteins determine the anatomy and metabolism of cells in the organism's various kinds of tissue throughout its development and viable existence, from conception to death.

Genome knowledge represents the apex of physiological research. Indeed, according to biology (the science of life), all instructions for adaptive functions are found in the genome. Therefore, no matter what the variations in the genetic makeup of individuals, health depends on how a person's genotype adapts within expression environments. This means the capacity for good health is unique to each individual. Since the "naked genome" does not exist, environment invariably serves as a selector. The result of this adaptive process is the phenotype — a visible, measurable (or at least assessable) entity. The fundamental genetic formula is $P \approx G+E$, where P is the phenotype, G the genotype and E the environments.

This formula is key to understanding the developments in genomics over the past decade and to anticipating the direction of future research. Until quite recently, research focused on the phenotype (P), which can be determined when, for example, an illness is diagnosed. Very recently, the genotype (G) has become the focus of related disciplines, such as proteomics and pharmacogenomics, which examine gene products in complex metabolic networks and how variations in DNA impact drug metabolism. As yet undeveloped are methodologies focusing on environments (E) and examining issues such as the impact of lifestyle on the demographic expression of genetic susceptibilities to common diseases.

Stages of the Human Genome Project

The advances in genomics since the late 1980s can be briefly described by identifying the five stages involved in developing this body of knowledge: (1) the creation of instruments for mapping the human genome; (2) the localization and identification of "key" genes; (3) the sequencing of genomes, particularly the human genome; (4) the examination of genotype-phenotype associations in complex multifactorial diseases; and (5) the assessment of the "genetic determinants of health" in populations, or population genomics.

As is often the case in science, these various stages have been facilitated by technological advances in the fields of molecular and cellular biology and bioinformatics. With each advance, new possibilities open up.

Mapping the Human Genome

Exploring a new continent requires maps, which are made gradually, beginning with the identification of major landmarks, followed by the filling in of details and, finally, topographic and geomatic information. The first genetic maps were based on the use of restriction fragments produced by the digestion of particular enzymes that intersect with DNA sequences in very specific locations. The action of these enzymes creates fragments of various lengths (RFLPs: restriction fragment length polymorphisms) that can be analyzed using electrophoresis and blotting — standard molecular biology techniques dating back to the 1980s. The analysis of these fragments often reveals individual variations known as polymorphisms that can be used as markers distributed across the genome at precise locations. Involving the use of isotopes, this technique is cumbersome and the number of markers limited. So the map created was quite sketchy.

In the late 1980s, Généthon in France used the new PCR (polymerase chain reaction) technique in conjunction with an older cell-fusion technique (human/rat fusion hybrids). This made it possible to identify a new class of genomic markers consisting of sequences with dinucleotide repeats. Thousands of markers distributed throughout the genome quickly became available to create the first map facilitating the systematic screening of the human genome.

This first-generation map was constructed using bioinformatics. Once certain markers had been identified as limits on various human chromosomes, bioinformatics made it possible to position the neighbouring markers correctly through the familial analysis of recombinations among the reference families of the CEPH (Centre d'étude des polymorphismes humains) in Paris. The computer technique for analyzing the link between two markers (either DNA sequences or phenotypes) had been developed in the mid-1960s. As a result, a second-generation map comprising almost 30,000 markers of all kinds was quickly created.

Identification of Key Genes

In the 1990s, the primary research objective in human and medical genetics was to locate and identify the genes associated with hereditary diseases and with the main proteins involved in cell metabolism and architecture. Since a location map was available and family studies promoted the use of link analysis, several key genes were located and then identified through sequencing. The mutation effect of these genes is sufficiently great to be observable or measurable in the form of phenotypes.

The previous technique, which involved using a purified protein (generally an enzyme) to determine the DNA sequence that codes for the amino acids comprising the protein, was supplanted by "reverse genetics" as of the mid-1980s. The paradigmatic example is the use of chromosome localization and sequencing to identify mutation Δ508 in the previously unidentified gene responsible for cystic fibrosis, whose function was unknown.

Traditional genetics examines the presence of specific diseases (phenotypes) in families and statistically evaluates the link between a phenotype and genome markers. The closer the marker is to the phenotype, the greater the likelihood that the responsible gene is nearby. By identifying these "genomic addresses," it is possible to determine the general location of a gene on a chromosome.

Once localized, the responsible gene must be located and identified by "walking" along the DNA sequence in the chromosome region. This involves the use of pieces of human genomic DNA packaged in viral vectors. These pieces are known as "contigs" because if placed end to end they would represent the entire contiguous genome. They are identified by the presence of the markers initially used to localize the gene in question. The final step is to sequence the contig or contigs to determine the gene signal and to validate this information by examining the distribution of the disease among the members of the reference families.

These approaches made it possible to, among other things, identify a new, previously unknown class of mutations known as dynamic mutations, found to be responsible for several diseases such as Huntington's disease and Steinert's disease, late-onset hereditary disorders.

Although somewhat effective in terms of the localization and identification of the genes responsible for hereditary diseases, these genetic maps did not cover the entire genome and proved to be of little use in the identification of susceptibility genes. Among carriers of such genes, the influence of the genetic variation (mutation) is not major but adds to the cumulative impact of other genes or varies depending on the impact of the expression environment of the gene in question.

Sequencing of the Human Genome and Other Genomes

By 1990, and in anticipation that the ultimate genetic tool would be a comprehensive map of the human genome, researchers in several countries proposed that the entire genome be sequenced.

The challenge was first taken up by the public sector, but the private sector in the United States quickly followed suit, launching a fiercely competitive initiative. The competition began with a discussion about principles. Should the initial focus be on sequences expressed in the form of proteins (ESTs: expressed sequence tags) because they come from "actual" genes in the form of messenger RNA and are therefore more important? Or should the genome be sequenced from A to Z, even though the vast majority of it was considered to be insignificant? (There was reason to believe this "insignificant" portion contained sequences regulating the opening, closing, and efficiency of coding genes.) The competition eventually led to the joint announcement in 2001 that a preliminary map of the human genome had indeed been produced.

Following the sequencing of the genomes of a number of organisms used in genetic research (such as yeasts, microbes, the fruit fly, and the mouse), it became clear that the entire human genome would have to be sequenced. Bioinformatics played an essential and central role in the production of this complete map. Once the genome had been divided into contigs, high-volume sequencing created a myriad of sequences, which then had to be pieced together by means of computer crunching based on new algorithms.

As the sequencing of various other genomes proceeded alongside that of the human genome, two new paradigms emerged. The first, which had already been tentatively confirmed, was the validation of the observed homologies between the genes of various species, including the mouse, the fruit fly, and the human being. Mouse/human homologies, even for non-coding sequences in the deserts between gene islands, were confirmed very recently, which has as yet unknown implications for the structural anatomy of the genomes. The second paradigm was the demonstration of the millions of variations in a single base pair (ATGC) at specific genomic addresses. Known as SNPs (single nucleotide polymorphisms), these variations may become the ultimate genomic markers, facilitating comprehensive screening. However, even new technologies such as "DNA chips," which can analyze millions of sequences on a microscope slide, are still too expensive. Nevertheless, the recent discovery that blocks of DNA sequences appear to be preserved within various human populations, varying by only a small number of SNPs for thousands of bases, suggests that three or four SNPs may be sufficient to assess the diversity of these long sequences. This would substantially reduce the costs of genomic screening. An international initiative has been launched to validate this approach by constructing a map of haplotypes (sequences of several SNP markers passed on from one generation to the next as unchanging blocks). Instruments that will permit the comprehensive screening of the genome are thus being developed and will be available for the penultimate step in the analysis of the human genome.

Complex Multifactorial Diseases

The new maps, the increase in the number of new markers, the identification of new genes at a geometric rate, high-volume sequencing technologies and bio-chips are now making it possible to search for the genetic variants that make individuals susceptible to common complex multifactorial diseases. Unlike the hereditary diseases associated with "major" mutations, which themselves make it very probable or even certain that disease will develop, the genetic components of complex diseases (such as asthma, hypertension, diabetes, certain cancers, and psychoses) often act in a limited way, but in conjunction with other factors, to increase the risks of disease depending on expression environments. These metabolic influences are part of complex, non-linear networks. It is thus important to identify both the innate and environmental components. In familial hypercholesterolemia, for example, even if an individual carries a mutation of the cholesterol receptor gene, other variations in the compensation or transport genes may limit the expression of the associated increase in cholesterol levels, as may lifestyle changes or preventive medication.

Since the genome contains all the biological information required to sustain life, it can be assumed that all diseases have genetic components, which does not mean they are hereditary. Cancer, for example, is a fundamentally genetic (not hereditary) event, because it is the genomic control of cell division that malfunctions.

So how should researchers approach the identification and characterization of the genomic variations likely to contribute to multifactorial diseases? To date, the analysis of linkages within large reference families and even within founder-effect subpopulations has failed to yield extraordinary results.

But the possibility of screening the entire genome to identify the variations thought to be associated with a particular phenotype has led bioinformaticians to develop associative statistical approaches. The genome of an individual with a disease is effectively superimposed on that of a healthy individual, and the regions where there are differences in their DNA sequences are then examined. The sample group can be made up of families whose sibships can be compared, or of large cohorts made up of patients with the same diagnosis. Since the causes of a single diagnosis can be heterogeneous, very large sample groups are required, unless the diagnosis can be made much more specific through the use of medical tests and very rigorous techniques. High blood pressure, for example, is not always caused by the same etiology. Even the presumed identification of a mutation associated with a complex disease in one population (sample) may not be validated in another population, where the cause may be a different variation in a different gene within the complex expression system of the multigenic and multifactorial disease. Such diseases result from an expression system, not from a major mutation in a specific gene.

Hundreds of laboratories and research teams around the world are recruiting patient cohorts based on clinical data in an effort to identify susceptibility genes. These cohorts can be drawn from multi-site clinical protocols or can be based on the medical records of an entire population, such as that of Iceland, or perhaps even Estonia or Great Britain.

Genomic techniques are constantly improving, in terms of the rate at which data can be processed. Genotype–phenotype association studies involving large cohorts should yield significant results in the medium term. However, it is important to bear in mind that the genomic variations identified as pathogenic components may vary depending on the particular populations and their history. The methodological approach is based in the first instance on the phenotype, which is then associated with genomic variations. By definition, and to ensure adequate statistical power, the sample is biased because it includes only individuals with obvious "diagnostic penetrance" and excludes carriers in the reference population who, due to other factors, do not present with the diagnosis.

However, a more accurate correlation between the genotype and the phenotype can be obtained by conducting subsequent epidemiological analyses of the socio-environmental and economic conditions of the cohort members.

This type of population genetics is primarily based on the examination of the relationship between a genotype and a phenotype followed by a traditional epidemiological assessment of the impact of environmental factors on cohort members. This is not a flawed methodology but rather the only means of identifying the genetic determinants of complex multifactorial diseases.

Population Genomics

Once all the variations associated with multifactorial diseases have been identified and the impact of genetic differences between populations has been taken into account, the next task will be to define their role in determining the health of an actual population. This is the final stage of the Human Genome Project.

The "innate relative risk" represented by a susceptibility gene for a disease, or by the side effects of medication, varies from individual to individual. It will be important to determine the demographic distribution of these susceptibilities and environments to facilitate decision making about health-promotion and disease-prevention programs, thus ensuring that health care resources are allocated more effectively. Furthermore, it is difficult to identify "protective variations" in samples comprising only people who present with disease, because there are few diagnostic tools designed to identify people in "better health."

Ultimately, the genes identified by "gene hunters" can be validated only within a non-biased population that has not been subject to any a priori stratification and thus has an even chance of representing a genotype found in the population under study. The sample must therefore include not only people in whom disease phenotypes are expressed but also "phenotypically healthy" people. The application of susceptibility variations on such a sample will reveal the prevalence of carriers, the proportion of penetrant carriers as well as the actual environmental conditions associated with the expression and non-expression of these variations. This will also make it possible to associate the protective or expression environments with the protective or risk variations.

The technologies and analytical methods are essentially the same as those used in the previous approach, but the sample is different. This approach is primarily epidemiological, involving the most comprehensive definition possible of the demographic, medical, social, and environmental situations of the participants, each of whom is chosen at random to represent the population as a whole. Following this epidemiological assessment, the known genomic variations obtained by research on biased cohorts can be applied to the random sample.

In short, this approach involves combining research on the genetic determinants of health with traditional epidemiological approaches to examining determinants of health in populations, such as the studies conducted by Health Canada and Santé Québec. Population genomics is thus a method that uses genomic research based on epidemiological data to demonstrate the distribution and prevalence of genotype–phenotype associations in populations, to both assess disease risk and protect public health. This scientific knowledge can therefore be used by various decision makers to establish programs designed to improve the health of the general public.

Population genomics is a new form of public health research whose unique feature is the capacity to assess individual diversity with regard to the distribution and examination of relative health risks within a population. The diversity of the "genomic" individual replaces the "average" individual of traditional epidemiology, holding out the theoretical promise of a personalized medicine that will respond to individual characteristics to prevent disease and maintain health.

Genomics, Health and Society

The advances in genomic knowledge and techniques over the past decade demonstrate that if genetic variations can be used to define a new approach to medicine, the various elements are in place to build this approach and employ it to facilitate better health planning for all members of the population.

The era of single-gene disorders is coming to an end; they just have to be identified, with the consent of the diagnosed individuals and of their families, by using definitive maps of the human genome to locate and sequence the key genes responsible.

The new frontier is complex multifactorial diseases, in which genetic factors interact with other environmental and socio-economic factors to create risk and then disease. Identifying and studying these susceptibilities will require more than just families. It will initially involve entire populations of people with disorders and then a much larger sample providing a significant representation of the actual general population — people with disorders as well as individuals at risk and not at risk.

Individual health is the momentary result of dynamic adaptation to development time and expression space. Health is a state of equilibrium, a homeostasis with regard to the power of selection. By definition, individuals possess their own unique adaptation limits, which means that all assessments of health are individual. Prior to the development of genomics, it was possible to discuss only the "average" state of health of a population, without being able to determine the range of risk variations for each individual. It is now theoretically possible to analyze and identify these variations.

To study the factors that promote adaptation (health) as well as those that lead to the expression of a misadaptation (disease), researchers will have to develop new generic analytical tools. Rather than creating cohorts based on particular disorders, it is necessary to establish a reference population in which all the genomic factors discovered by researchers around the world can be attributed to individuals and validated in their specific environments, which have themselves been characterized using appropriate epidemiological and sociological methods. This generic resource will thus become a crucible for the importance of susceptibility genes in health care planning for an entire population. Furthermore, as a research tool, this resource will make it possible to identify "protective genes" that tend to elude cohort-based approaches.

Creating a significant non-biased sample representing an entire population is costly, because all the individuals recruited to represent population segments must be assessed, questioned, and identified with regard to their various living environments using standard methods. The results must then be evaluated by comparing them with general databases on the population as a whole to ensure that the sample is completely valid and truly representative of the population under examination. Such an approach can thus be used only in societies where good-quality health, census, and environmental data are available.

This type of population genomics involves multidisciplinary methods that combine biological techniques and bioinformatics with human and social sciences, even in the design of the protocols themselves. Since the research deals with human populations and societal objectives, new ethical standards must be developed to provide for the prior consultation of the general public, to protect the participants and the entire population, as well as to define the public interest, including the obligation to share the benefits with society as a whole. The family or cohort studies used in the past did not have to comply with such stringent standards, because the guidelines for research of their scope are designed to protect human subjects as individuals but not as citizens and members of a given population.

Conclusion: First Understand, Then Decide

The hypothesis that genetic determinants of health may have a significant impact on public health and the health care system in general applies only to developed countries with the social infrastructures required for genotype–environment correlation studies. Although the results of such studies will be applicable in all countries, programs and resource planning must be based on actual data on the population in question. Actions and decisions cannot be taken in response to demands for services based directly on biased research samples, at least in the case of programs aimed at the entire population rather than particular families or individuals.

Already, the clinical services and genetic counselling provided to individuals and families fail to meet known needs. This is primarily due to the fact that decision making within health care systems is still influenced by the findings of traditional epidemiological research, which quite rightly assesses health determinants in relation to socio-economic environments. Traditional epidemiology has yet to develop methods that factor individual risk into the general equation used to produce measures of the average state of health. Nor can traditional epidemiology deny or invalidate the impact of these individual components, because they are not included in its calculations.

Modern genomics can now provide traditional epidemiology with the means and methods required to refine its equations and averages, because genomics can aggregate and stratify the genetic components of risk in a population.

This new expertise is certain to make epidemiological analysis more complex. New statistical and computer methods will have to be developed to take genetic diversity into account. It is also important to bear in mind that health genomics is defining a new frontier that promises, in the long term, to provide a better understanding of adaptive phenomena between individuals and the other genomes that influence us, such as those of microbes — or even between individuals and toxic environments or medications, not to mention sociological phenomena such as poverty.

Finally, awareness of the distribution of individual health factors within the population may eventually promote personal responsibility and empowerment with regard to health, making public health the result of the individual decisions of citizens.

The Economics and Business of Genomics

Ron Yamada

Introduction

"Achieving Excellence," Canada's Innovation Strategy document, provides a challenging framework inviting Canadians to contribute ideas to improve the economic and social fabric of Canada. If the goals outlined for 2010 are to be achieved, the growth of new industry sectors, as well as existing ones, must be accelerated.

This session invites discussion about bridging the transition from developing intellectual property to dealing with the economics and business of genomics to build large successful businesses.

Companies, such as MDS, recognize the immense importance of the increased investments in research and development made by federal and provincial governments. The work of Genome Canada, the Canadian Institutes of Health Research (CIHR), and the Canadian Foundation for Innovation (CFI), complemented by the efforts of the Natural Sciences and Engineering Research Council (NSERC), and the National Research Council (NRC), just to mention a few, has advanced basic research throughout Canada. Industry and researchers alike have been particularly pleased that there has been no pause in the increase of investments in research.

Each province has also been an active supporter. As an example, Ontario, has tripled its contribution to research funding. Programs such as the Ontario Research Challenge and Development Fund, the Premier's Research Excellence Awards recognizing scientists, and the Ontario Innovation Trust, have advanced scientific inquiry.

Industry must improve its ability to transfer the results of scientific inquiry. Working with scientists, it must create, not just new companies, but new industries with global markets.

The biopharmaceutical industry is embryonic in Canada today, but is in a globally competitive position with respect to the number of companies. At present, there are over 350 biopharmaceutical companies in Canada. But Bio2002 will serve as a powerful reminder of the global nature of the competition to discover and develop new, more effective drugs.

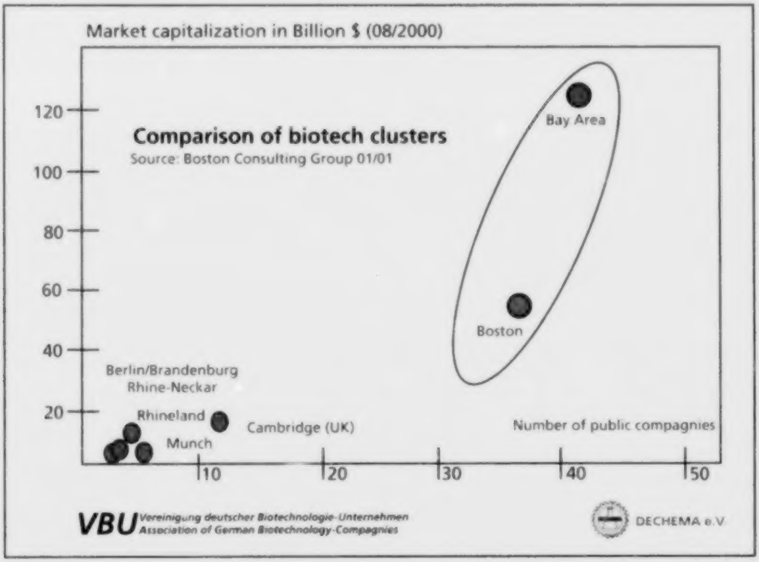
Biotechnology clusters in Germany, the United Kingdom, the United States, the Nordic countries, and increasingly in Singapore and France, have companies that are developing compounds, which will compete directly and indirectly with those in Canadian biopharm companies.

Leading research agencies in the United States are doubling their research budgets. Many states are deploying windfall tobacco money to support biotechnology. Michigan and New York for example, have committed a billion dollars each in this area.

In Europe, the Joint Research Centres (JRC) have just announced that drug discovery and development will be a key area of focused support in its sixth framework for research. The total JRC budget for the period 2002 to 2006 is 17.5 billion euro.

These examples illustrate that it is not just numbers; *it is size and scope that is essential for success.* To put this in graphic perspective, Figure 1, based on numbers provided by the Boston Consulting Group, shows the location and market capitalization of biotech clusters, in $20 billion increments on the Y-axis, and the number of companies on the X-axis.

Figure 1: Location and Market Capitalization of Biotech Clusters



As a Canadian company, MDS wishes to continue to contribute to the growth of Canadian industry, and to try to advance the country's Innovation Agenda.

MDS's 10,000 employees serve two customer groups: health care providers, and pharmaceutical and biotechnology companies. MDS assists health care providers in the prevention of illness, and in the rapid diagnosis and treatment of their patients.

For pharmaceutical and biotechnology companies, MDS provides global, leading edge, services, products, and information to help customers develop their drugs faster.

The management of MDS Capital Corp and its $1billion of investments and funds provides important insights for new therapeutics, diagnostics, and information, in health and life sciences.

We are fortunate to be involved with leading researchers, and to be able to invest in exciting new science-based companies. As one of the world's largest suppliers of services and products to pharmaceutical and biotechnology companies, we are able to understand the challenges and opportunities in drug discovery and development. Providing diagnostic services to over 40,000 doctors in North America gives us an understanding of clinical practice and new needs.

Much of the following discussion is based on the observations and experiences that we would like to share with you today.

The Challenge

This panel has been charged with debating the challenges and identifying solutions to establishing successful genomic-based companies. Among the major challenges identified are long lead times requiring patient capital, complex ethical issues, and the slow evolution of new regulatory processes.

The potential rewards are, however, even more significant. Successful companies will export products that contribute to health care. Pharmacogenomics offers the possibility that drugs may be customized for classes of patients, for increased effectiveness, thereby reducing health care costs.

By being able to continue to manufacture these new drugs in Canada, new technology-based skills will be developed. The non-cyclical nature of the biopharmaceutical business will encourage reinvestment in research and greatly increased collaboration with academic centres. Another advantage would be the ability to attract more highly qualified personnel and capital to Canada.

We will be able to leverage our investments in research and development, and venture capital. The multiplier effect is large.

So there is much to gain...and much to lose.

Issues and Possible Solutions

So how might we collectively accelerate the evolution of a competitive base of companies to a large industry sector, and what might we learn by examining the pharmaceutical model?

One is struck by the benefit of indigenous large pharmaceutical companies in the development of biotechnology companies, particularly in countries such as Sweden. There, Pharamacia and Astra continue to support biotechnology companies. In Europe and the United States, indigenous pharmaceutical companies are active participants with government in strategies to develop the biotechnology sector, and are involved in their implementation. These companies are an important source of experienced science and product trained managers.

Drug discovery and development is a high-risk, difficult, and costly process. It requires scientists experienced in compound evaluation to select one from many for development. Knowledgeable evaluation of compound activity, metabolic characteristics, formulation, and toxicity, as well as analysis of competitive compound and market size is required before qualifying a drug for further development.

Once qualified, product management becomes a key focus. Experienced product managers employee a "best of breed" approach to accelerate the drug's development by selecting proven internal or external providers of service and products to lower cost and reduce time to market.

By having many compounds under development, a pharmaceutical company can offset the failure of some compounds with the success of others. It is this ability to manage risk that has contributed to the pharmaceutical industry having a 30 percent return on investment.

Is there structural weakness in Canada, which could prevent the Canadian pharmaceutical sector from maximally exploiting its current position? Could this slow the development process and, in turn, prevent the development of a successful, job-creating sector, with Canadian manufacturing of products exported to global markets?

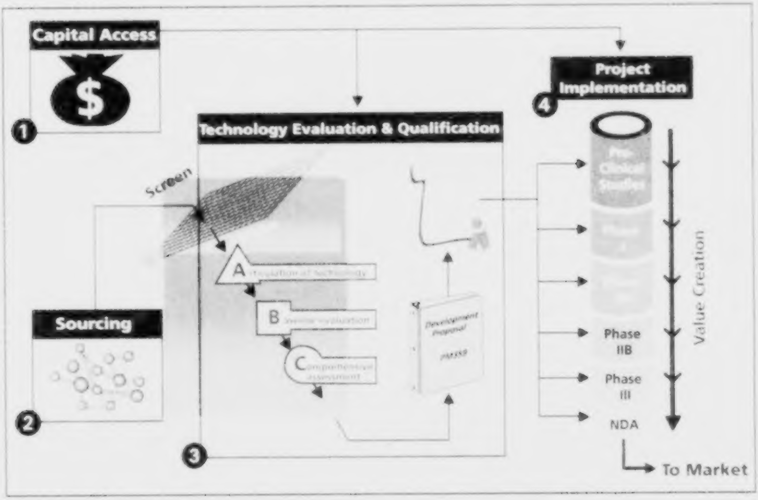
Could we increase the success rate of drug development and reduce the risk of failure by taking a portfolio approach that assesses all compounds in all biopharmaceutical companies in Canada, and by accelerating the development of all quality compounds? By 2010, will Canada have a large number of small, healthy biopharm companies, or will it have a significant number of large successful companies, as well as a growing group of successful smaller companies, all rapidly developing their products?

The former is a recipe for the hollowing out of the biopharmaceutical industry, and not realizing the benefit of research and development investments.

The latter offers the possibility of export revenues, expanding tax revenues from growing corporations and their employees, enabling additional research investments.

Figure 2 illustrates the process of screening compounds, and the discovery and development steps required for a drug to be approved for clinical use. Figure 3 shows the relationship between risk and value creation as the selected compound moves along the development process.

Figure 2: Approval Process


Capital Access
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Technology Evaluation & Qualification
Screen
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B
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Comprehensive assessment
Development Proposal
Sourcing
2
3
Pre-Clinical Studies
Phase IIB
Phase III
NDA
Value Creation
To Market

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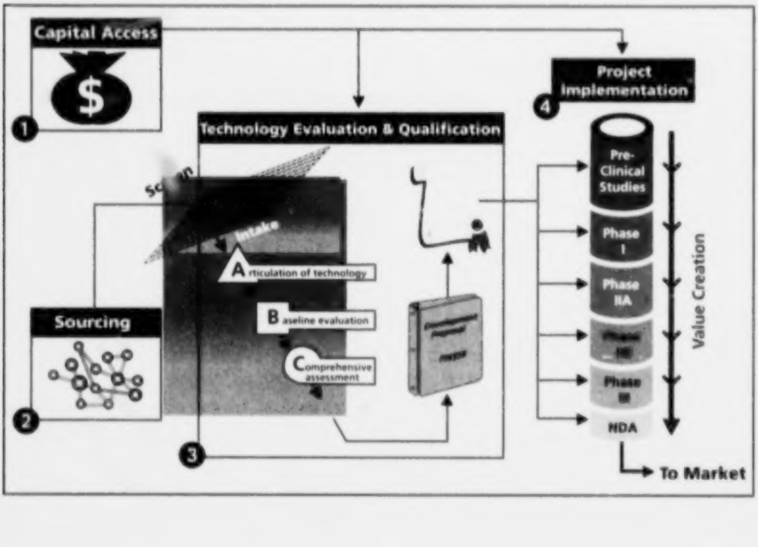
Capital Access
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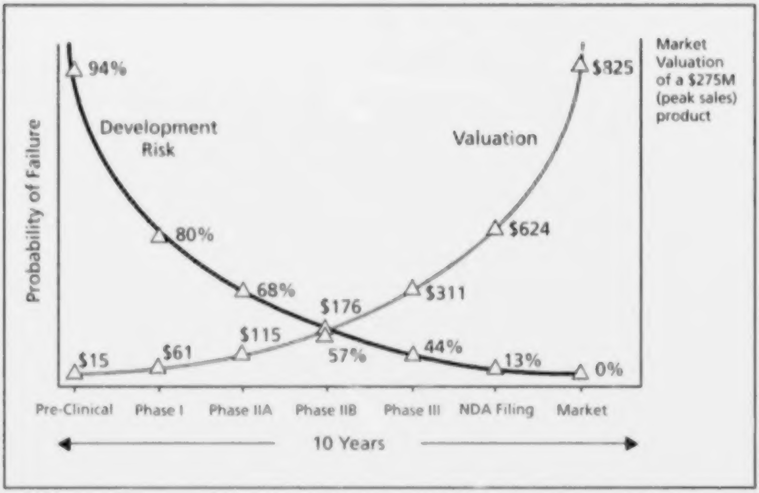
Pre-Clinical Studies
Phase I
Phase IIA
Phase IIB
Phase III
NDA
Value Creation
To Market

Figure 2 illustrates the systematic evaluation of tens of thousands of compounds conducted by pharmaceutical companies, before qualifying those, which have the characteristics to be a successful drug. This evaluation follows an established methodology, and includes the activity of a compound against a target disease, its absorption, and metabolic characteristics, its formulation possibilities, and its toxicity profile.

Only in following such a qualification does a drug become a candidate to enter the complete drug discovery (preclinical) and the drug development (clinical trials) process.

Excellence of product management and most efficient use of external infrastructure is a key ingredient for success. Figure 3 demonstrates the value appreciation curve as the drug proceeds through clinical trials, using a model of a drug with peak sales of approximately $275 million, as a base. It is for illustrative purposes only, and is meant to show how the risk of failure is lowered as a drug moves through the various stages of drug discovery and clinical trials, how the value of the compound increases, and the long gestation period for a drug to be approved for sale.

Figure 3: Example of Risk vs. Valuation for an Average Drug



The preclinical or drug discovery stage is a period of high risk, as those in the industry know. However, as one begins the drug development process, or enters Phase I, which is testing the safety of the drug in healthy volunteers, the value of a compound begins to increase. At the point that a drug completes Phase II, where efficacy has been demonstrated in several hundred patients with the target disease, the risk and valuation curves often intersect.

Our challenge is to increase both the number of compounds in drug development and the rate of development to Phase IIB and beyond. A process to evaluate all the compounds of all the biopharmaceutical companies in Canada, and accelerate the development of selected compounds will increase the chance of success.

Compare this for a moment to what typically happens to biopharm companies in Canada. While there may be four or five compounds, or multiple uses for the same compound within a biopharm company, the focus is usually on one lead compound, and there aren't enough financial or scientific resources within the individual company to evaluate other portfolio compounds to the same degree. Ironically, the selection of only one compound increases the risk of failure.

Consequently, many of these compounds are either not developed or prematurely licensed out before any value has been created.

Raising capital takes an inordinate amount of the scientist/CEO's time. Once raised, the capital is too often used to build costly and time consuming infrastructure, as opposed to using existing external resources to speed development.

Allelix offers a sobering lesson as an example of a successful small biotech company that could not raise additional capital, even to support a new compound demonstrated to enhance bone growth. Its stock price declined, and it was ultimately acquired by an American biopharm company, which saw the benefit of the family of compounds developed by Allelix.

Biomira and Hemosol, both public companies, have multiple uses for their platform technology, and two or three other compounds, which are not being developed due to a lack of both human resources and financial capital.

How can we offset a possible infrastructure weakness, and develop all the quality and effective compounds in all the biopharm companies in Canada?

We offer the following suggestion.

First, establish a process to evaluate all the compounds in all the biopharmaceutical companies in Canada. Where applicable, compounds in development in academic centres in universities and research-based hospitals should be included. An expert team comprising a mix of scientists, clinicians, and market specialists experienced in compound evaluation methodologies and drug development would evaluate the available data, and assess markets for compounds. As part of the evaluation process, key development milestones would be identified for each selected compound.

The result would be a pipeline of compounds, which would enter an accelerated drug development process.

While ownership of the compound would continue to lie with the biopharmaceutical company, this process would use best of breed suppliers of infrastructure and would be enabled by timely access to capital. This drug accelerator would increase the value of compounds by moving most efficiently through Phase I to Phase IIB, and position the compound and the biopharmaceutical owner to negotiate the most advantageous agreement to enter the most costly part of the approval process, Phase III.

In all selections, whether it be in choosing the expert team, or the providers of service, a competitive process is recommended. In the case of providers, risk sharing would be anticipated, with respondents being required to commit capacity and/or investments to increase commitment.

To ensure timely access to funds to support an accelerated development process, a self-renewing source of funds is needed. Since this would be a national initiative, it is recommended the federal government, in partnership with the private sector, *establish the evaluation process and a self-renewing innovation development fund (IDF), with the private sector creating a matching sister fund.*

The objective of the fund would be to maximize the value of drugs, by accelerating development from investigational new drug (IND) to Phase III. Access to the IDF and the sister fund would have a number of conditions. For example, to qualify for funds, an experienced lead investor, such as a venture capital firm, would be required, with the other funds providing up to 50 percent of the total funding.

The process for qualifying drugs and related milestones offers the venture capitalist an opportunity to understand the opportunities for additional rounds of financing if milestones are met. This should contribute to the attraction of "patient" money for the duration of the drug development process. Since the IDF would participate in the increase in valuation at each financing round, the opportunity to realize gains, and reinvest the gains, has the potential to make the IDF a self-renewing fund.

The self-renewing fund would ensure the most effective use of existing infrastructures. As previously stated, where external resources were used, a competitive bidding or qualification process would be required.

The amount needed in the fund would depend in part on the number of quality compounds, but needs to be of sufficient size to accelerate development of a Canadian biopharm industry.

Experience has shown that success in compound development can attract additional capital. By developing a portfolio or pipeline of compounds, one increases the chance of success, resulting in a financial engine for sector growth.

We believe the expertise exists in Canada to conduct such evaluation, and a creative combination of federal and private sector capital can be used to create such a self- renewing fund.

Catalyzing the growth of Canadian biopharmaceutical companies can result in a strong biomanufacturing industry in Canada. This leverages investments in research and venture capital, and builds a strong competitive infrastructure, in an industry which will grow with research in proteins and the evolution of pharmacogenomics, resulting in drugs for more effective treatment of selected categories of patients.

A recent CIBC World Markets report indicated that today, there are only 18 compounds from Canadian biopharm companies in Phase III trials. We can do better.

With our combination of outstanding science, a base of existing biopharmaceutical companies in Canada, and private sector capabilities to fund and develop products, action today will lead to a significant contribution to the national economy, to the health of Canadians, and to patients around the world.

Genomics and Public Policy: The View from Europe

Noëlle Lenoir

With hopes and fears: That's how Europeans guage genomics.

Expectation one for Europeans is the promise of cell or gene therapies, for example, drugs derived from biotechnology to cure diseases such as cancer, cardiovascular ailments, and Parkinson's or Alzheimer's. They also expect pharmacogenomics to allow doctors to prescribe drugs in a more individualized way, thus avoiding lethal side effects. Expectation two is that genetic testing or screening will integrate genomic information in preventive medicine and public health — the way, for instance, screening techniques supported by a major educational program for clinicians and the public helped eradicate thalassemia in Cyprus a decade ago. And last, Europeans expect that genomic information will foster more responsibility in individuals, allowing them to know how to act in their own best interests when faced with future health problems.

But Europeans are also fearful. Some refuse purely and simply to see life, especially human life, turned into a commodity. They are the main opponents to what they call "patenting life." And they're the ones who are worried about the risk of stigmatization and discrimination induced by genetic testing and screening. As you all know, European opposition to genetically modified (GM) foods and crops has had an important impact on commercial relationships between the United States and the European Union. What makes this a particularly delicate issue for politicians is the fact that people are both fascinated and worried by biotechnology. Society's reaction to progress in life sciences is partly emotional, but partly political too. Why?

Let me first point out why Europeans sometimes don't embrace genomic advances. Second, I want to insist on the complexity of European federalism, which makes it hard for governments to initiate and push ahead with research and development in genomics. Third, it's clear that genomics has definitely helped redefine common European ethical values. Last, I emphasize the way Europe is now stepping up its performance in genomics and, I must admit, trying to close the gap with the United States.

Why Do Europeans Have Ethical Concerns About Genomics?

Let's look at history. Although the younger generations are much less attuned to European history than those born after the war (such as me), for many Europeans genetic research still revives horrific memories of medical experimentation carried out by the Nazis. This explains the deep-rooted fear of eugenics and why eugenic practices, such as reproductive cloning, are banned in Europe either by European Community law or by national legislation. Indeed, there is hardly any discussion of this ban, the legitimacy of which is largely recognized. If European society is more secular than American society, it nevertheless holds that "not everything is allowed" contrary to what Dostoevsky says in *Crime and Punishment* and that science is due to have limits.

The Old World concern with the manipulation of life is also rooted in age-old cultural traditions. The Judeo-Christian tradition and the romantic tradition inspired by the German philosophers and poets have greatly shaped Europeans' views on the sacredness of life and nature. Ecological dogma partly derived from this romantic view of Mother Nature means any "artificial" human intervention to manipulate life is potentially dangerous or even disastrous. Which would explain why European Greens and Christian Democrats very often vote the same way to limit research in biology and genomics.

Above all, political reasons also explain European criticism of the present trend of genomics. The rise of ecological awareness goes hand in hand with the rise of globalization. And for some Europeans, patenting genes, or cells in particular, symbolizes blind market forces where money rules everything. Yet don't forget that in Europe social rights, in particular the right to health protection, are enshrined, and European governments are expected to ensure free access to health care. Such an attitude has prevented European pharmaceutical industries from competing with those in America or Japan, to the detriment of European health care. Indeed that was never the intention!

How to Deal with the Complexity of European Federalism with Regard to Genomics?

Now just a word to tell you about the peculiarity of the European Union as a federal system. You Canadians and Americans are used to this system, but we poor Europeans have neither a constitution, nor a European government. Yes, we have a common currency. And yes, what is still more important, we have common rules of law, which are directly applicable in all European member states. European legislation has teeth, since it is backed by national courts as well as by the European Court of Justice in Luxembourg, all of which give precedence to European rules over national ones.

But what a real tangle! European federalism is too complicated for words. The limits of power of the European Community are not exactly clear. Moreover, European authorities are exercising some form of jurisdiction in more and more areas. For instance, although the European Community has, in principle, not an iota of power to regulate research or medicine, to name all the areas related to genomics in which European regulatory powers have been exerted, is impossible. Having to lay down regulations for the free circulation of goods and services on the common market has justified the adoption of extensive European regulations in the field of genomics, in such areas as patenting life, the voluntary dissemination and confined use of genetically modified organisms (GMOs), the circulation of human tissue and organs, clinical trials, and data protection. All these issues are now dealt with by European legislation. They have still to be combined with national rules concerning sensitive subject matter, such as embryo research. But these national rules are becoming less and less important as more and more topics are dealt with at the EU level.

It has to be admitted that the combination of European and national rules can result in a very peculiar situation which recalls the American system and what's sometimes called a "double standard." Take embryonic stem cell research, for example. In Germany and France, where embryo research is forbidden by law, the free market principles of the European Community have been invoked by the governments of these countries to justify importing embryonic stem cells for national research needs. This is very similar to the way President Bush has tackled the issue in maintaining the ban on the federal funding of embryo research, while at the same time allowing the National Institutes of Health (NIH) to use embryonic stem cell lines belonging to private laboratories.

How Europe's Approach to Genomics Has Resulted in the Redefinition of Common European Ethical Values?

Paradoxically, despite the diversity of opinions in Europe toward the progress of life sciences, the adoption of European regulations in this field has fostered reflection on common European values. In a way, the quite reluctant attitude of Europeans toward genomic development has brought about the building of Europe as a moral and political community.

"European ethical principles," as stated in some European regulations, are key to understanding the European approach to genomics. Among these principles, human dignity, "which is inviolable" according to European law, plays a particular role. Unlike in the United States, individual freedom is not always number one and, sometimes, human dignity takes a back seat to individual freedom. The prohibition by European law of "reproductive cloning" and of "eugenic practices" illustrates this.

Data protection, such as individual genetic data, for instance, is also part of European legislation. One piece of European legislation, based on the right to privacy, dating back to 1995, forbids data flow to countries "which do not provide an adequate level of data protection," namely the United States according to the Europeans. And I can assure you that this doesn't go down very well with Americans regarding their international trade requirements.

European legislation also mentions the prohibition of "any discrimination based on genetic characteristics." How this provision will be applied is yet unknown. But, for the time being, all European insurance companies have decided on a moratorium and are abstaining from asking for information about test results for their clients.

I won't comment on the ethics of patenting biotechnological inventions, since the ongoing debate in Europe is confusing at best. Indeed, it has been a European hallmark since the beginning of the 19th century. The first European legislation or treaties on patents affirm that inventions contrary to "public order and morality" shall not be patentable. What does that mean and are patent offices prepared to apply such ethical principles? Certainly not.

How Do European Governments Strive in This Context to Tackle the Challenge of Genomics?

Americans usually think that Europeans' reluctance toward GM foods and crops hides protectionism against American imports. This is only partially true. It is true that most European farmers are keen on sticking to their traditional methods and do not see GMOs, especially those imported from the United States as having any interest for them. They likely overestimate the risks linked to GMOs while underestimating the danger to human health from the large use of pesticides. But farmers or even members or sympathizers of the Greens, who feel nostalgia for pastoral agriculture, are not the only ones to oppose GMOs. In the post-mad cow era, European citizens have some reason for food fears. With regard to the application of genomics to medicine, I'm not sure that we, in Europe, are more sensitive than the Americans or the Canadians to the possible risks. What makes the biggest difference, in my view, is that in the United States in particular, ethical concerns are secondary compared to scientific and industrial challenges. In a country like the United States whose founders were pioneers, science is a value in itself, and economics is the main mover of society. And it is not a criticism since I note this with admiration. The basic reason for the impetus of a country like the United States seems to be a culture driven by innovation and entrepreneurial risk. The US culture and tax environment encourages risk taking, much more than in Europe. The rush to patents illustrates this tendency to transform research into business. And it's thus not surprising if it is less accepted in Europe than in the United States. But things are changing. European governments are aware that a civilization which does not innovate is due to disappear. They know that only knowledge-based economies will survive or succeed. They know that without robust scientific research, Europe's moral and intellectual independence will be in peril. Last but not least, they have in mind the European Treaty objective of ensuring the highest possible level of health for all Europeans. This implies taking up the challenge of genomics to fulfil these promises.

That's why European governments are progressively launching programs to strengthen the position of life sciences in economics. The United Kingdom, which is at the forefront of this sector along with Germany, has been involved for a very long time in this field. But it's amazing to see how Germany, whose research was quite late and where biotech companies were very weak a few years ago, has easily filled the gap, having surpassed British scientists in the number of pending patent requests. They have quite a number of companies listed on the stock exchange where they had none some years ago. The French government is now following the same way. I've been asked to draft a report — which I recently handed over to the government — to suggest a course of action to foster the biotech sector in France. I was so astonished to see that the government was not even opposed to allocating fiscal advantages to support innovative projects and the creation of business in the biotech sector! Quelle générosité! Another French revolution, and a cultural one this time!

But still more important is the impulse from the European Union whose framework program of research (2003-2006) makes biotech and life sciences the priority of priorities. The adoption of this program by the European Parliament has occasioned heated debate on ethical issues, such as germ line therapy or therapeutic cloning. But in my view it's perfectly legitimate that the legislators of Europe want to discuss these very sensitive subjects. Science and ethics are perhaps less difficult to reconcile than we imagine. Ethics means that we have a duty to be vigilant. It means transparency of biomedical practices and discussion that is open to the public on all these practices, not just the most talked about on TV programs.

What perhaps is more difficult is to reconcile access to health care, which in Europe is deemed a constitutional right, with the development of costly genomic research which will lead to efficient but necessarily costly medical treatments. This is a democratic issue and, to be frank, no one in Europe really knows how to deal with it.

Social health care and genomics — that's "another story," as Kipling said — too tough for me to chatter on about here. That's why I suggest we come back to Toronto another day to discuss this. The Canadian health care system has a very good reputation and perhaps you've the key to solving the problem.

Part 2

Genetic Medicine and Privacy

Genetics and the Environment in Human Health: A Balanced Approach

John Frank
Geoffrey Lomax
Patricia Baird
Margaret Lock

Introduction

Enthusiasm for discovering genetic correlates of health and disease is currently widespread. This enthusiasm is encouraged by a combination of recent research initiatives, such as the Human Genome Project, and the flurry of media reports announcing that yet another gene–disease association has been identified. Implicit in all these activities, and explicit in many, is the notion that one can attribute health and disease to genetic determinants and that understanding the genome will lead, inexorably, to improvements in population health.[1] The new insights provided by advances in human genetics are exciting, because genes hold the codes for molecules that carry out biological processes. Thus, genetic research provides a molecular level of analysis for the study of diseases and their causation. For example, powerful new genetic research techniques allow the researcher to document the molecular changes that occur when a benign cell is transformed into a malignant (cancerous) one. This level of information is proving invaluable in the management of lung and colon cancer (Fong et al., 1999; Dubois, 2000).

Information at the molecular genetic level has greatly informed disease diagnosis and management of individuals with inherited conditions due to single genes ("Mendelian conditions"). However, these breakthroughs will be counterproductive if they distract attention from other forms of disease causation, especially social structure, physical environmental influences, and lifestyle factors,[2] which are of great importance for the common diseases of industrialized life, all of which are "genetically complex" (i.e., the product of many genes interacting with the environment over entire lifetimes).

The tendency toward an emphasis on clinical interventions in the new genetics leaves us skeptical that elucidating genetic determinants of disease will imminently lead to improvements in population health. Our skepticism arises from experience suggesting that interventions involving broad-based genetic screening are profoundly difficult to implement and have a limited impact on population health. Further, we are concerned that a disproportionate emphasis on genetic determinants leads us to overlook the importance of population health research: research and policies directed toward the full complement of social, environmental, and lifestyle determinants of health.

Enthusiasm for research linking gene expression to health and disease is understandable. As a branch of risk factor epidemiology, it lends itself to relatively tightly controlled study, and genetic correlates are more easily grasped than the complex notion of a web of physico-chemical, biological, social, economic, and personal factors interacting over the life course to cause disease. Yet modern epidemiologists have for decades utilized the metaphor of "webs of causation" in explaining the origins of human health at the population level (MacMahon and Pugh, 1970). It is important, therefore, that powerful and intuitively appealing genetic mechanisms be viewed as only part of this web. It is also critical that genetic technologies be applied and used wisely, and their limitations recognized, so they are not made the object of unrealistic expectations. If the potential of genetic technology is overestimated, it may be applied inappropriately, with resultant harm, or at minimum with waste of scarce health care resources (Baird, 2000).

We argue that knowledge of the actual determinants of human health, at the population level, and especially the role of social structure, environment, and lifestyle, should lead to rather modest expectations of a "genetic silver bullet" approach to improving population health status. This argument, in turn, has two main themes.

- Most common diseases in technologically advanced societies are multifactorial in origin, by which we mean that they are the product of complex interactions between our genetic endowment and the world around us, acting over the course of a human lifetime.

- There are profound difficulties in attempting to actually implement broad-based genetic screening and intervention programs at the population level, of the sort that would be required if the new genetic knowledge were to radically alter disease frequency in entire societies.

The Multifactorial Nature of Human Disease

A key observation about rates of disease, and indicators of health, is that they are astonishingly variable across populations. Consider the so-called chronic diseases, such as cancer and heart disease that are the principal causes of death in developed nations. Schottenfeld and Fraumeni (1996) documented ten to twentyfold differentials in site-specific cancer incidence rates around the globe, particularly for the most common cancer sites in "westernized" populations with high life expectancy: breast, colon, prostate, lung and bladder. In some cases we know a great deal about why these rates differ. For example, lung cancer's relationship to smoking, at both the population and individual levels of analyses, is common knowledge. However, even for tumors where we cannot currently explain more than a fraction of cases by known causal exposures in the environment, such as breast and colon cancers, occurrence rates may vary by more than ten-fold. (Schottenfeld and Fraumeni, 1996) This is true even from region to region within those wealthier nations that have sophisticated cancer surveillance registry systems that produce reliable statistics at the level of the sub-national region.

What might proponents of genetic disease determination say about such differentials? It is likely they would look for varying genetic characteristics across these differently affected populations, for example in tumor suppressor/ promoter gene frequency and/or expression. On the other hand, the public/population health scientist would point to the dozens of published migrant studies in the last few decades as evidence of the clear environmental influence on these disease rates.

Geographic Variation in Disease Occurrence and Migrant Studies

Migrant studies take advantage of immigration to compare the disease experience of the immigrant groups with that of their countries of origin and destination. Many of these studies have shown that, over time, immigrants shed the chronic disease patterns of their country of origin and take on those of their country of destination. For instance, significant changes in chronic disease rates, including cancer incidence, occur within a generation or two of migration from low-incidence settings to high-incidence settings, and vice versa (Schwab, 1998). Genetic differences could not possibly provide the primary explanation for this phenomenon, since genes do not change that quickly in populations! Furthermore, the gene pool of migrants generally changes very little over the first few generations after migration, due to persistent intra-marriage within the migrant community after arrival in the new homeland.

High-quality migrant studies demonstrating these patterns abound in the epidemiological literature, but appear to have been largely overlooked by genetic researchers. A well-executed epidemiological migrant study of disease occurrence is analogous to, but constitutes a distinct improvement upon, the "twins reared apart" study design used by many genetic researchers to help disentangle genetic from environmental influences on health and function (Plomin et al., 1990; Reiss et al., 1991). In both study designs, genetics is held constant, while environment is changed. In migratory studies, substantial variation in environmental conditions is guaranteed by the constraint that study subjects have moved from one country to another. In twin studies, all that can be guaranteed is that the twins do not live together. They may, in fact, live in the same region or in different regions where the disease rates of interest are similar. Thus, well-designed migratory studies are a more reliable source of information on the influence of environmental factors, "holding genetics constant," than studies of twins reared apart.

Table 1 summarizes several influential migrant studies of coronary heart disease (CHD) and of the major cancers of the industrialized world conducted over recent decades. These studies demonstrate large increases in the rates of disease within two generations of immigration to "high-risk" countries, from "low-risk" countries and, occasionally, the reverse pattern in those moving from high- to low-risk settings.

Table 1: Selected Migrant Studies of Chronic Disease

AA Author(s)	Study Design	Findings	Conclusions
Ziegler et al. (1993)	Population-based case control of Chinese, Japanese, and Filipino aged 20-55 migrating to SF-Oakland, Los Angeles, and Oahu.	A six-fold gradient in breast cancer risk by migration patterns was observed.	Migrants with 8 or more years in the West had a relative risk of breast cancer 1.8 times the risk of migrants with 2-7 years.
McCredie et al. (1990)	Breast cancer rates in migrants to NSW, Australia from various European countries, compared to native-born women.	Relative risk for Italians changed from to 0.5 to 1 over a 17-year period. Risk for Welsh changed from 2.75 to 1.5 over same period.	Rates in groups with previously higher and lower relative risks move toward risk levels of new homeland after migration.
McCredie et al. (1990)	Colon cancer in migrant males and females to NSW, Australia from Italy and Greece compared to native born.	Relative risk for Greeks and Italians changed from 0.2 to approximately 0.8 over a 17-year period. Change is less in Italian women: 0.2 to 0.6.	Immigrant patterns are converging on native patterns.
Marmot and Syme (1975)	Mortality from CHD in Japanese from Japan, Hawaii, and California.	Age-adjusted prevalence rates for definite CHD were Japan 5.3, Hawaii 5.2, and California 10.8/1000.	Japanese in California were converging on native California experience.

The point of this table is that the most widespread, serious diseases of modern life, all of them conditions more common among older adults, seem to be extraordinarily sensitive to environmental influences. And there is abundant evidence that environment in this case includes both physical exposures and social/psychological experiences. An illustrative example of the role of the environment is given below. The practical public health implication is obvious: some environmental effects, such as nutrition, acculturation, and lifestyle, are clearly reversible, since migrants to high-risk areas are protected from these effects only one generation before migration, and a few thousand miles away.

Finnish Height Study

It is often thought that the extent of genetic transmission of a trait — its "heritability" — is clear-cut, quantifiable, and fixed. But this is not the case. Heritability differs from environment to environment. It can be expressed in a statistical index (ranging from a value of 0 to a value of 1) reflecting the proportion of the variation in the characteristic or condition that is genetically transmitted among individuals in a defined population. It can be derived from a variety of study designs, including studies of monozygous (identical) and dizygous (fraternal) twins. An elegant Finnish study of height clearly demonstrates that complex gene–environment interactions make the heritability of even a "simple" human trait, such as height, highly context-sensitive.

The Finnish study utilized an established national twin registry with 33,534 pairs of adult twins, born before 1958, and both still alive in 1974. (Silventoinen et al., 2000) Using data from two mailed questionnaires on height and factors determining zygosity, 3,466 identical and 7,450 fraternal pairs of twins were analyzed. The results showed a clear trend in the heritability of height across the following birth cohorts: those born before 1928; 1929 to 1938; 1939 to 1946; and 1947 to 1957. The heritability of height steadily increased during this period of gradually improving living conditions in Finland, from 0.76 to 0.81 in men and from 0.66 to 0.82 in women. This fits with global data showing that in developing countries with widespread malnutrition and infectious diseases associated with sub-optimal child growth, heritability of height is generally lower (e.g., 0.56 in one West African study by Solomon et al., 1983). Thus, the degree of genetic determination of this basic human trait is not a constant, but will vary in different environments.

Genetic determination is greatest when environmental factors adversely affecting height are least prevalent, and least when these factors are most widespread. This contextual "relativity" of causation in human biology has long been described by epidemiologists (Rothman, 1986; Pearce, 1996, 1999).

It is due to the fact that we can only observe the influence of those causal factors that *vary* in given settings. The role of genetics in determining height (and many other human attributes and conditions) is not fixed, but subject to alteration in the face of different environmental circumstances, such that our genetic height "potential" cannot always be realized in our actual living conditions. The net genetic determination observed in a study of a specific population, such as Finns over the last century, is inevitably "filtered" through that population's environmental exposures.

The Thrifty Gene

This idea that the observed genetic contribution to a specific trait in a population is always filtered through environmental exposures is important. As we suggested in the example of cancer, differential rates of disease within and between populations tend to be attributed, in the first instance, to genetic factors. The problem is that this simplistic view of the meaning of disease variation may distract attention from the complex processes actually at play.

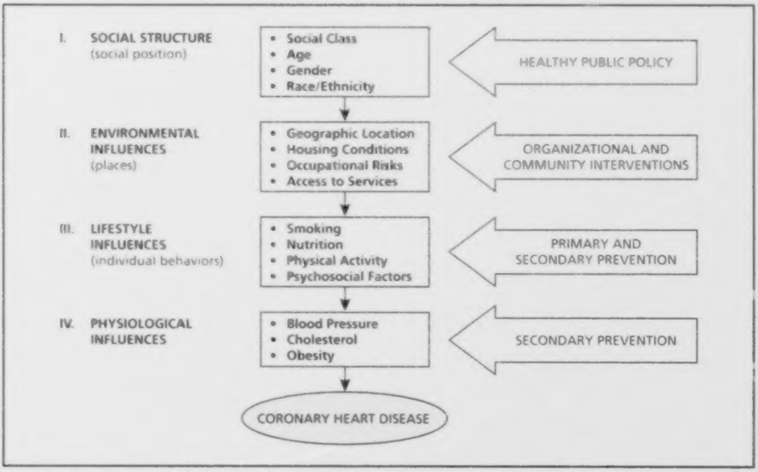
Consider the observation of a clustering of non-insulin dependent diabetes (NIDDM) in certain ethnic groups in the South Pacific. This clustering has been attributed to the existence of a thrifty genotype that enabled the carrier to use food more efficiently during times of famine, but is less of an asset now than in the feast-or-famine days of hunting and gathering, and seafaring cultures (Neel, 1999). The underlying hypothesis is that the thrifty genotype only became a risk factor for NIDDM when the food supply became stable and more than adequate. But, as more and more people have been exposed to the western lifestyle of the late 20th century, it has become clear that obesity and NIDDM are the response of diverse populations, regardless of whether a specific thrifty gene is present (McDermott, 1998). A high intake of energy-dense refined foods (animal fats and sugar) combined with low fibre levels and a lack of micronutrients from fresh fruits and vegetables — the typical dietary pattern of individuals in lower social classes living a western lifestyle — appears to be the high risk scenario for NIDDM. The nutritional influences of the environment filter the expression of the genetic predisposition to NIDDM. However, an imbalanced focus on genetic determinants of the condition in affected ethnic groups diverts attention from more appropriate dietary interventions that can actually pre-empt or reverse NIDDM. The genes matter, but they were always there. What has changed, rapidly, is the environment.

Coronary Heart Disease

This brings us to the central reason why profound preventive impact will not readily result from genetic technology for coronary heart disease, most cancers, and chronic diseases in general: these diseases are all profoundly multifactorial. For example, CHD, which is still the major killer in the developed world and the top cause (after childbirth) of hospital admissions in most countries, has over 20 known independent risk factors of biological significance,[1] only a few of which are primarily genetically determined.

Figure 1 summarizes, without intending to be exhaustive, the levels of causation currently known or thought likely to independently affect the occurrence of CHD, categorized according to their position in the causal pathway. More "upstream" (or "exogenous") risk factors, such as social position and environment, are distinguished from more intermediary risk factors, such as blood pressure or cholesterol levels. The latter are biological characteristics that are under "homeostatic" control in the human body. That is, they are regulated by internal feedback systems that are influenced, in turn, by a complex range of factors from the external environment and the internal milieu. These mechanisms are, in turn, controlled in part by our genetic endowment, and in part by cumulative environmental influences throughout life.

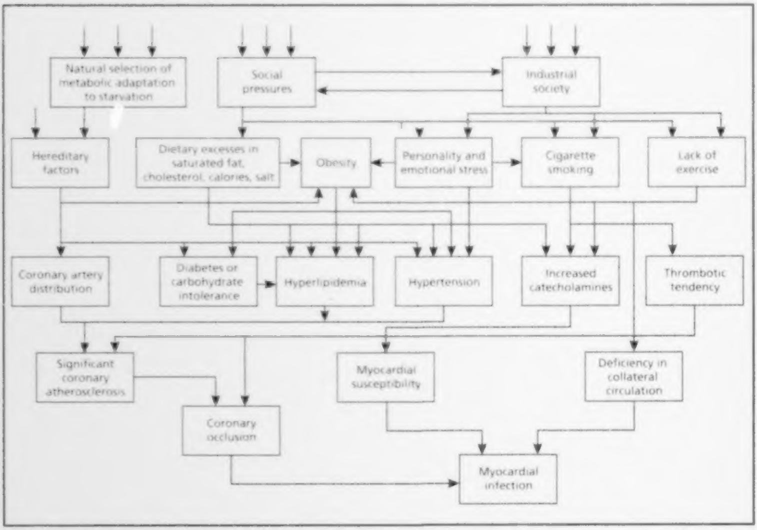
Figure 1 – Levels of causation of coronary heart disease and corresponding types of health intervention


I. SOCIAL STRUCTURE
(social position)
• Social Class
• Age
• Gender
• Race/Ethnicity
HEALTHY PUBLIC POLICY
II. ENVIRONMENTAL INFLUENCES
(places)
• Geographic Location
• Housing Conditions
• Occupational Risks
• Access to Services
ORGANIZATIONAL AND COMMUNITY INTERVENTIONS
III. LIFESTYLE INFLUENCES
(individual behaviors)
• Smoking
• Nutrition
• Physical Activity
• Psychosocial Factors
PRIMARY AND SECONDARY PREVENTION
IV. PHYSIOLOGICAL INFLUENCES
• Blood Pressure
• Cholesterol
• Obesity
SECONDARY PREVENTION
CORONARY HEART DISEASE

Source: McKinlay and Marceau (1999).

The interrelationships between these many established levels of influence, all of them putative "causes" of CHD, are so complex and so poorly understood that we are aware of no recent publication that attempts a comprehensive "causal path diagram" depicting them. It is instructive, however, to examine such a figure published over a decade ago by Gary Friedman (1987) in his textbook, *Primer of Epidemiology*. Complex though it is, many recently discovered risk factors, such as perinatal characteristics, anti-oxidant intake, and recent antibiotic use, are absent from this schema (Danesh et al., 1997; Jha et al., 1995; Mattila et al., 1998). However, one can readily see that the full "causal web" for CHD, even as currently understood, probably involves interactions among these and dozens of other cofactors acting over the entire life course. Again, only a small subset of them is primarily genetic in determination.

Figure 2 – The web of causation for myocardial infarction: a current view


Natural selection of metabolic adaptation to starvation
Social pressures
Industrial society
Hereditary factors
Dietary excesses in saturated fat, cholesterol, calories, salt
Obesity
Personality and emotional stress
Cigarette smoking
Lack of exercise
Coronary artery distribution
Diabetes or carbohydrate intolerance
Hyperlipidemia
Hypertension
Increased catecholamines
Thrombotic tendency
Significant coronary atherosclerosis
Myocardial susceptibility
Deficiency in collateral circulation
Coronary occlusion
Myocardial infection

Source: Friedman (1987).

The Contribution of Sir Geoffrey Rose

Fortunately, a conceptual framework has been advanced that places these causal processes in a broader context. It was proposed by the British cardiovascular epidemiologist Sir Geoffrey Rose, in his landmark paper "Sick Individuals and Sick Populations," published in 1985. Rose pointed out that risk factors for chronic diseases, such as CHD, can be thought of as either conferring risk, because they shift *entire* human populations' distributions of exposure, or because they shift an *individual's* position within a particular societal distribution of exposure. For example, serum LDL cholesterol can be thought of as conferring more CHD risk on some individuals in Western countries than others, according to whose measured levels are higher or lower. However, the entire bell-curve distribution in Western countries has been so enormously shifted upward that even relatively "low" individual LDL cholesterol levels in these populations confer considerable CHD risk, compared to the markedly lower distributions of LDL cholesterol in most developing countries. Rose pointed out that research which seeks to identify only the determinants of an *individual's* level of this CHD risk factor, compared to those of others nearby, will literally "miss the forest for the trees." Only through comparison with samples of individuals from pre-industrial populations, whose cholesterols are not shifted upward en masse, can the true nature and underlying causal factors of the modern epidemic of CHD in richer nations be understood.

Most common diseases today show a very strong inverse gradient by social class (Evans et al., 1994). As noted above, the common fatal diseases of our society are due to interactions between genotype and environmental factors. Yet genotypes do not differ strongly by class.[1] Rather, marked class differences in disease incidence are due to different exposures to environmental "triggers." Genes affect *who* may get sick within a class if exposed, but environmental factors, such as those listed above for CHD, determine the *relative frequency* of sickness across social classes. Rose went on to make many useful points for those who would seek to change dietary, exercise, and other human habits at the individual level of intervention. He warned that only modest impacts on population-level disease burden can ever be expected from approaches targeted at particular individuals who are "outliers" on the societal distribution curve for the risk factors. The best we can do is to therapeutically "truncate" the high end of the risk curve by risk factor modification. To substantially reduce a population's level of chronic disease, one needs to seek the causes of incidence that shift entire risk factor distributions at the population level, not simply the causes of cases at the individual level.

For our discussion here, however, there is another implication of Rose's pioneering conceptual framework. It turns out — as Rose noted — that for many chronic disease risk factors (including serum lipids, blood pressure, and perhaps serum levels of key "toxic" or protective nutrients, such as folic acid/homocystine), the determinants of entire populations' distributions of risk are largely environmental, while the factors affecting an individual's level of risk, within any population, are much more likely to have a genetic component. An example has been provided in data from controlled trials of lipid-lowering diets for high cholesterol individuals (Denke, 1994; Denke and Grundy, 1994). These trials have shown that only 30 to 50 percent of treated individuals have a substantial serum lipid response to dietary management — one that primary care doctors would consider successful as first-line treatment of elevated LDL cholesterol (Ramsay and Yeo, 1991). Other persons are not very responsive to diet; and genetic factors are thought to be important in this difference.

Many persons with elevated lipids are genetically sensitive to diet, and our culture has evolved to expose virtually all of us to unhealthy diets. Sijbrands et al. (2001) examined mortality over two centuries in a large pedigree with "familial hypercholesterolaemia," a condition which leads to high serum LDL cholesterol arising from mutations in the low density lipoprotein receptor gene (Sijbrands et al., 2001). Mortality in the pedigree was lower than the general population in the 19th century, but rose after 1915 to reach a peak in 1950. Sijbrands et al. suggested that raised low density lipoprotein concentrations may have protected people from infectious diseases that were more common in earlier centuries, but the absence of environmental risk factors, such as widespread cigarette smoking, high fat diet and sedentary physical activity patterns in the 19th century may have been equally important. In other words, the decline in the former class of threats and the rise in the latter over the past two centuries transformed a low risk state into a high risk state. Today, the many citizens of affluent societies with high cholesterol have that condition due to environmental conditions *peculiar to their specific historical and cultural context*, interacting with their individual metabolic/genetic constitution (Kaprio, 2000).

The point is that gene–environment interactions codetermine the most common chronic and lethal diseases. The way in which genes and environment interact to cause the major diseases of our time is such that patients with overwhelmingly "genetic" conditions or overwhelmingly "environmental" conditions are relatively infrequent. Rather, occupying the top positions in the rank orderings of major public health problems are conditions where both genes and environment interact, such as heart disease, stroke, cancer, and diabetes.

Even the effect of smoking, which is a clear environmental hazard for individuals who smoke and those around them, differs in interaction with genetic constitution. It has been known for decades that not all smokers suffer equally from the health consequences of their habit. Indeed, basic scientific research demonstrates several genetically mediated mechanisms by which some smokers develop lung cancer, chronic obstructive lung disease, and other adverse health consequences of the habit, while others do not. Rose (1985) himself pointed out that, if we happened to live in a society with universal smoking, lung cancer would be regarded as a largely genetic disease. So even a clear "environmental" risk factor like smoking has genetically co-determined health effects. Even though the elimination of smoking would be very beneficial to the population overall, some individuals would not benefit as much as others, as they are less likely to suffer detrimental consequences from tobacco smoke exposure in the first place, presumably on a genetic basis (Haugen et al., 2000).

The environmental co-determination of most chronic disease means that increased genetic knowledge, enabling more powerful genetic interventions, will not be sufficient to broadly improve population health. Such interventions are not likely to have a major impact unless we start to die, or become disabled from, very different causes than we do today. Purely genetic manipulations undoubtedly will confer specific health benefits on those at very high risk for largely genetic reasons (e.g., "single-allele" conditions such as Huntington's Chorea, some familial hypercholesterolemias, or haemochromatosis).[5] The fact is, single allele conditions are quite rare (<0.1 percent prevalence) (Baird et al., 1988). But to understand the conditions from which most people suffer in their later years, and due to which they "shuffle off this mortal coil," will require a combined genetic and environmental approach. The multiplicity of causal pathways to the common chronic disease end points of adulthood, and the complexity of interacting factors over the life course, make it unlikely there will be a widely applicable "genetic magic bullet" for these diseases. Indeed, emerging evidence indicates that such diseases have their roots in pre- and perinatal life, and in early childhood, due to complex gene–environment interactions "embedding" themselves in human physiology, leading to frank disease decades later (Barker and Medical Research Council, 1992; Barker, 2001).

Problems in Moving from Science to Society: Some Examples of Difficulties in Genetic Program Implementation at the Population Level

A typical layman's response to news of any genetic advance, particularly the discovery of a "new gene" associated with a specific disease, is that we can soon expect "breakthroughs" that will reduce the disease's impact on society. Implicit in this expectation is the belief that widespread screening for, and/or genetic manipulation of, the defective gene will bring net health benefits. However, a few examples reveal that "there are many slips 'twixt cup and lip" in the practical use of genetic technologies to improve health across entire populations. This is especially true among persons currently well, who are only at risk of future illness. For these people, genetic screening may not only be ineffective, but may actually cause substantial harm.

Breast Cancer Genes

There can be little doubt that the discovery of the BRCA1 and 2 genes in recent years has led to numerous requests for breast cancer screening by women and their physicians. This has constituted a substantial additional workload for the health care system, in terms of assessing women's risk, counselling them appropriately, and testing those who can genuinely benefit. Does this constitute a cost-effective use of resources to reduce the incidence of breast cancer? Existing reviews and recent studies (Ford et al., 1995; Langston et al., Tambor et al., 1997; Lock, 1998; Collins, 1996; Elwood, 1999a,b; Lerman et al.,1997; Lynch et al.,1997; Malone et al., 1998) suggest the following reasons to doubt that this new clinical genetic activity will markedly reduce the future incidence of breast cancer.

- Early estimates of the proportion of all breast cancers occurring in carriers of these two genes (now believed to be less than five percent, although it is slightly higher among cases under age 35) were substantially inflated. This was because genetic investigators based their estimates, uncritically, on studies of high-risk families. They did not employ proper epidemiologic techniques to reduce the potential for bias in generalizing the experience of very atypical (high-risk) families to the broader population, so other unidentified genetic and environmental risk factors in these families crept in and artificially inflated their risk estimates. Thus even if it were possible to completely remove the effects of these two genes there would be little impact on breast cancer rates in the population.

- Similarly, early notions of the frequency of these genes in the general population were exaggerated. It is now clear, for example, that BRCA1 occurs in only 0.12 to 0.2 percent (12 to 20 per 10,000) women in North America. Thus, even if it were possible to offer lifelong tamoxifen or raloxifene to all carriers, and have them comply with such chemoprophylaxis, population-based screening efforts to identify women with these genes would be extraordinarily inefficient — 2,500 individuals would require testing to prevent one case of cancer (Vineis et al., 2001).
- Furthermore, even if screening the whole population of women were seen as desirable from a societal perspective, there are disincentives to being screened from the perspective of the patient. For example, it has been found that even among proven, multi-case BRCA1 carrier families, only 43 percent of women invited for testing participated fully and wanted their test results. Of the remainder, fear of loss of health insurance was a major reason given for refusal of testing, or for having testing without wanting results personally.
- Even simple screening decisions themselves may have adverse psychosocial consequences for persons merely offered screening. Among the women in the carrier families, six-month follow-up revealed a decline in depression among those tested and found to be non-carriers, no change in those testing positive, and an increase in depression among the substantial subset who had declined testing.
- Women in families that have been affected by breast cancer tend to greatly overestimate their own risk of the disease, and their misapprehensions are not reduced by intensive counselling from a trained genetic educator. Analogous effects on the broader population of low-risk women, if screening is offered to them, are a matter of speculation at present.

The point of these findings is *not* that BRCA1 and 2, or similar gene testing, has no place in the rational and compassionate management of breast cancer risk among high-risk families. Rather, the public health concern is the balance of risks, benefits, and costs of widespread unrestricted use of these tests, beyond their selective use in women with clear-cut positive family histories of breast cancer. The spread of testing is of special concern since low-risk women's anxieties about breast cancer will inevitably be exploited by commercially oriented testing labs seeking to expand their market (Lock, 1998). Therefore, there is reason to be concerned that the demand for such "breast cancer gene" testing in the general population will greatly exceed the medically justifiable indications for test utilization (Elwood, 1999a,b). This is worrisome, in that the risks and costs of such "low-risk" testing would predictably exceed any potential health benefits. In short, there is much potential for both harm and wasted health care resources, and precious little promise of net health benefits, as a result of overly enthusiastic utilization of such technology.

Fortunately, in this case the cautionary perspectives of evidence-based medicine and public health coincide. But it is not clear that this will be enough to restrain the market for screening.

Fragile-X Syndrome

In 1995, the American College of Human Genetics issued guidelines for testing for the gene for Fragile-X syndrome.' The guidelines included recommendations that all males and females with any physical or behavioural characteristics of the syndrome, individuals with a family history of the disease, and those asymptomatic individuals deemed to be "at risk" for this disease should be tested (1995). The incidence of Fragile-X syndrome is estimated to be about one per 1,500 males and one per 2,500 females (Warren and Nelson, 1994). It is associated with mental impairment and mild learning difficulties or hyperactivity; though the latter is often estimated to be in the normal range (Brown et al., 1993). In common with a good number of other so-called genetic diseases, the involved genes exhibit "incomplete penetrance" (i.e., not all individuals with the genotype will manifest the disease, for unknown reasons). It is estimated that about 20 percent of males and 70 percent of females with the mutation express no symptoms, making the designation "at risk" extremely problematic. Moreover, the severity of symptoms varies enormously, and cannot be predicted. Benefits from therapeutic and educational interventions have not been shown (Caskey, 1994).

In 1993, a Fragile-X testing program was put in place in the Colorado public school system as part of an effort to develop an inexpensive test that could be used as a model for a national program (Hubbard and Wald, 1993). The project, funded by Oncor, a private biotechnology company, was carried out by a university–industry consortium, and was explicitly designed to save later public expenditure on children with mental deficits. Before the program was set up, a report was published by the Colorado Health Sciences Center and the University Business Advancement Center that argued that screening could enhance economic efficiency. Estimated cost to families and also public expenditure used for care of Fragile-X patients was carefully calculated, and the conclusion was that "the savings to the state would be tremendous" from implementation of a screening program (Lauria, 1992).

The research team developed a checklist of "abnormal" behavioural and physical characteristics associated with the disease, including hyperactivity, learning problems, double-jointed fingers, and prominent ears. They tested selected children, but not in a clinical setting. After two years, the program failed to turn up the anticipated number of cases, was deemed uneconomical, and suspended (Hubbard and Wald, 1993). Yet the impact on the lives of those children who did test positive was significant, including becoming targets of discrimination by health insurance companies. Ironically, even though the predictive quality of the test was uncertain, many parents not only co-operated, but actively encouraged its use. At the time, a report by the Office of Technology Assessment noted that the finding of a "genetic underpinning" to various behavioural and psychiatric problems has given "enormous relief to many families" (Flynn, 1993). This cautionary tale demonstrates that population-based genetic screening programs can readily develop a momentum of their own, driven by political, economic, and cultural forces, without regard for the actual risks and benefits to participants.

Pre-Implantation Diagnosis

There are many fields of medicine, covering the whole life cycle, where genetic identification may be applied, even starting before embryo implantation in the uterus, for example. If in vitro fertilization is carried out, the early embryo can be genetically tested before it implants. A cell may be taken from the cluster of cells making up the zygote and genetic probes used to identify particular genes, or the chromosomes may be examined. Only those embryos without an identified "undesirable" genotype may then be transferred to the woman's uterus.

The number of instances where it is appropriate to offer pre-implantation diagnosis (PID) is extremely small. This is because most common diseases are not determined by single gene or chromosome abnormalities. Further, it is only appropriate to offer pre-implantation diagnosis where a couple has already been identified as being at increased risk for having a child with a particular serious single-gene or chromosomal disorder, since it is necessary to know what condition to test for. This identification will usually be made because of the previous birth of an affected child. But such couples already have the option of prenatal genetic diagnosis for those disorders where PID might be used, and prenatal diagnosis is far less costly, more accurate, and has fewer health risks for the woman. This reduces further the proportion of pregnancies where it is appropriate to offer PID — it is relevant only for people unwilling to have prenatal diagnosis for example, for religious or personal reasons.

In spite of the above, private clinics providing this technology can be expected to market and promote it, since the more services they provide, the more successful they are as businesses. In 1997, a private fertility clinic in Toronto offered to screen embryos for risk of "genetic disease" before implantation for a fee of $6,500 to $9,800 per cycle of treatment. It offered PID to the public for 27 "genetic" diseases — some of which show no close correspondence between a single gene (allele) and the disease (e.g., breast cancer) (Mitchell, 1997). The clinician involved said: "This is the beginning of the end of genetic disease" and added that the roster of diseases the clinic would identify could grow dramatically over time, and this should have "the same impact antibiotics did to bacterial disease." This kind of promotion and hyperbole markets the technology as "quality control for parents" and is likely to lead to inappropriate overuse. Less invasive, less costly approaches are available for those couples at high risk, who wish to avoid having a child that is affected by a particular serious genetic disease. Simply letting the market decide how genetic testing at this stage of life will be used is likely to lead to misleading promotion and unwise use.

Prenatal Diagnostic Testing

Expansion of prenatal diagnostic testing, as mentioned above, is another example of a potentially unwise use of genetic testing. This may occur if its use is expanded beyond serious single gene-determined disorders, as it has been used to date, to conditions where the role of genes is less clear. There are rapidly increasing numbers of genes that have been, and continue to be, identified through the Human Genome Project. Increasingly, genes "associated" with particular traits, or conferring an "increased risk" of a disease can be identified, and a growing range of genes "related to" various traits and susceptibilities can be detected. In view of the incentives for doctors and laboratories to provide ever more testing services, prenatal testing for a range of such genotypes could become widely disseminated unless they are regulated to ensure that the costs, risks, and benefits have been rigorously established.

Genetic risk information for diseases with complex causal pathways, such as most cancers and CHD, usually comes in the form of probabilities. As noted above, semi-quantitative phrases such as "associated with," "increased risk," and "related to" are used in this context. It is clear, from the environmental risk perception literature, that probability statements have limited meaning for most people even when they are not being manipulated for marketing purposes. Thus, the public may not readily understand that having a particular gene does not inexorably lead to having its "related" disease, depending on intervening lifelong exposures. Letting prenatal genetic testing develop ad hoc is a recipe for letting anxiety and marketing trump sober analysis. Most people would like to have healthy children and marketing of prenatal diagnostic testing could play into that natural aspiration in an exploitative and misleading way. People are understandably susceptible to such marketing, feeling they "should do all they can to have a healthy child." If it is to bring health benefits to a population, prenatal testing should only be offered in programs with clear protocols, with demonstrated benefit, demonstrable expertise, and resources for counselling and follow-up.

On a Brighter Note: Promising Genetic Interventions

Having provided the above precautions for population-wide genetic interventions, we return now to the genuinely promising potential for understanding and managing multifactorial diseases that result from the interaction of genes and the environment, and are of great public health importance. There are several such conditions for which we are on the verge of quantum leaps in our understanding of how they may be prevented — and new genetic technologies are playing a critical role in expanding this knowledge (Zimmern 1999a,b; Kaprio, 2000). In the cases given below, genetic insights serve a dialectical purpose. That is, knowledge of the relevant genes and their functions allows us to characterize, with much greater precision, the *environments* in which they create increased risk. Thus, genetic insight leads, in the first instance, to the opportunity for environmental remedy.

Asthma

Asthma is a disease characterized by an abnormal immunological response to environmental stimuli. There are over 17 million Americans with asthma — including almost five million children — and their numbers are increasing. Indeed, the very fact that major increases in the frequency of asthma have occurred in recent decades is proof that a considerable portion of its determination cannot be purely genetic. It is estimated that asthma-related costs exceeded $14.5 billion in the year 2000. Several specific gene–environment interactions have been implicated as risk factors for asthma (Holgate et al., 1995; Holgate, 1999). For example, an association is reported between HLA genes and susceptibility to toluene-diisocyanate-induced occupational asthma (Mapp et al., 2000). This knowledge clearly has public health relevance, because it enables us to further elucidate the web of causation that, in this example, should inform environmental changes — substitution of hazardous chemicals and improvements in exposure control measures. As more and more genes are defined and their function in relation to the expression of allergic disease established, a major task will be to assess the relative importance of each gene and integrate the complex series of genetic and environmental factors into a coherent understanding. Primary exposure prevention will generally be the most efficacious method for promoting a healthy population. In this scenario, genetic information in aid of individually targeted environmental preventive measures is secondary.

Nutrition and Tuberculosis

Tuberculosis is turning out to be the largest single infectious cause of death, globally, between 1990 and 2020 (Murray and Lopez, 1997). Susceptibility to disease after infection is influenced by environmental and genetic factors. Epidemiological evidence suggests a link between vitamin D deficiency and tuberculosis (Bellamy, 2000). Vitamin deficiency generally results from inadequate dietary intake. However, the vitamin's protective effects may also be influenced by genetic variation in the vitamin D receptor gene. Preliminary research suggests that tuberculosis risk increases tenfold in patients with a genetic variation that influences the serum concentration of vitamin D metabolites (Wilkinson et al., 2000). However, these patients represent a small portion of all tuberculosis cases and the gene variation is relevant only under conditions where the individual is likely to be exposed to the TB pathogen. Such conditions are increasingly rare in the established market economies, where genetic technologies are accessible, but highly prevalent in less developed regions where TB is still rampant (Murray and Lopez, 1997). Clearly, the nutritional health of the population in general is paramount in reducing tuberculosis. Genetic information, in this case, serves to inform specific dietary supplementation in limited populations, such as health care workers in communities with large immigrant populations, but the impact of this intervention on the overall burden of disease will be modest at best.

These examples demonstrate that current advances in our understanding of genes–environment interactions will almost certainly improve our capacity to prevent and treat subsets of some common multifactorial diseases. Targeting specific environmental and lifestyle changes to reduce risk and developing individually tailored therapies (pharmacogenomic tools) for sick individuals are easily foreseeable. However, widespread genetic testing must meet stringent criteria for both proof of safety and preventive effectiveness, and for the protection of the rights and privacy of those tested. It must also be judged against the opportunity cost of forgoing measures, such as pollution controls, tobacco use reduction, or agricultural and food-marketing policies, which would improve the environment generally, and benefit the health of the whole population.

Conclusion

The determinants of most common diseases are complex, with environmental and genetic/biological factors interacting over the life course, embedded in a social context. Focusing exclusively on the genetic strand of this intricate web of causation, although profitable for some, will not address many other important disease determinants. An overemphasis on genetic approaches is particularly likely to lead to a passive neglect of environmental codeterminants of health, and not likely to be the best way to better the health status of the population. There are forces in our society (biotechnology-pharmaceutical industries, testing service providers and labs, those wishing to deny the role of socio-economic factors in health determination, etc.) pushing for a genetic approach to ill health, and this means we are at risk of not using genetic technology in an appropriate and balanced way. However, there is promise that, if we can achieve an appropriate and balanced use of new genetic technologies, we will improve our understanding of how genes and environment interact to cause many common diseases. Such a goal would be in the spirit of Rose's maxim to "seek causes of incidence"(in populations) rather than simply the "causes of cases" (among individuals).

Notes

1 For example, at a recent OECD workshop one speaker claimed about 70 percent of cancers and cardiovascular diseases are due to inherited susceptibility. See Vineis et al. (2001).

2 Note these *levels of causation* are frequently aggregated as *environmental influences*. Here environment refers to the influence of places. The distinction between social, environmental, and lifestyle is useful, because each requires a distinct type of health intervention. See McKinlay and Marceau (1999).

3 By the term "biological significance" is meant that there is a moderate "strength of association" (REF-Bradford Hill) between the risk factor and an incident CHD outcome (as measured by the relative risk of disease occurrence with the risk factor present, compared to that risk without the risk factor's presence.) This means that the relative risk of disease is, say, two or more for dichotomous risk factors, such as gender. (Or this can be calculated from the inter-quartile "dose" of continuous risk factor. This is the amount of exposure equivalent to the difference between an exposure distribution's 25th and 75th percentiles in a given study population, for a risk factor measured on a continuous scale, such as blood pressure or serum cholesterol.) The term is used to distinguish risk factors with strong enough disease associations to constitute "substantial" prima facie evidence of causation, from those with mere "statistical significance" but dubious biological *substantive* significance in a given study.

4 It is difficult for social classes to become strongly associated with genotypes unless there is stable and complete marital isolation of each class for thousands of years, which has not been possible, at least in Western industrialized countries. Alternatively, if marital selection were strongly associated with heritable traits (e.g., only blue-eyed spouses were thought suitable mates for blue-eyed suitors) one could envisage those traits becoming highly associated with certain population groups. But social class, while often the subject of formal marriage taboos in many societies, has rarely proved such an impassable barrier for human affection in the long run.

5 New population-based evidence suggests that the commonest gene for this last disorder actually causes clinical symptoms in only one out of 150 homozygotes, suggesting that previous estimates of the gene's "penetrance" (predictive validity for disease) were far too high, due to over-generalization for high-risk families studied (Bleutler et al., 2002).

6 The Fragile-X syndrome, the most common form of heritable moderate mental retardation, and second most common among all causes of MR, after Down's Syndrome, in males, has a frequency of 1 in 4,000 male births. It is due to multiple excessive (over 200) repeats of a single DNA base-pair triplet, CGG, located in the 5' untranslated region of the first exon of a gene called "FMR1" on the X chromosome leading to loss of gene function (Nussbaum et al., 2001).

References

Baird, P.A. (2000) "Genetic Technologies and Achieving Health for Populations," *International Journal of Health Services*, 30(N2): 407-424.

Baird, P.A., T.W. Anderson et al. (1988) "Genetic Disorders in Children and Young Adults: A Population Study," *American Journal of Human Genetics*, 42(5): 677-93.

Barker, D.J.P. (2001) *Fetal Origins of Cardiovascular and Lung Disease*, New York: M. Dekker.

Barker, D.J.P. and Medical Research Council (Great Britain), Environmental Epidemiology Unit (1992) *Fetal and Infant Origins of Adult Disease: Papers, London: British Medical Journal.*

Bellamy, R. (2000) "Evidence of Gene–Environment Interaction in Development of Tuberculosis," *Lancet*, 355(9204): 588-589.

Bleutler, E., V.F. Felitti, J.A. Koziol et al. (2000) "Penetrance of 845G_A (C282Y) HFE Hereditary Haemochromatosis Mutation in the USA," *Lancet*, 359: 211-218.

Brown, W.T., G.E. Houck et al. (1993) "Rapid Fragile-X Carrier Screening and Prenatal Diagnosis Using a Nonradioactive Pcr Test," *Journal of the American Medical Association*, 270(13): 1569-1575.

Caskey, C.T. (1994) "Fragile-X Syndrome — Improving Understanding and Diagnosis," *Journal of the American Medical Association*, 271(7): 552-553.

Collins, F.S. (1996) "BRCA1 — Lots of Mutations, Lots of Dilemmas," *New England Journal of Medicine*, 334(3): 186-188.

Danesh, J., R. Collins et al. (1997) "Chronic Infections and Coronary Heart Disease: Is There a Link?" *Lancet*, 350(9075): 430-436.

Denke, M.A. (1994) "Individual Responsiveness to a Cholesterol-Lowering Diet in Postmenopausal Women with Moderate Hypercholesterolemia," *Archives of Internal Medicine*, 154(17): 1977-1982.

Denke, M.A. and S.M. Grundy (1994) "Individual Responses to a Cholesterol-Lowering Diet in 50 Men With Moderate Hypercholesterolemia," *Archives of Internal Medicine*, 154(3): 317-325.

Dubois, R.N. (2000) "Review Article: Cyclooxygenase — A Target for Colon Cancer Prevention," *Alimentary Pharmacology & Therapeutics*, V14(SUPP1): 64-67.

Elwood, M.J. (1999a) "Public Health Aspects of Breast Cancer Gene Testing in Canada Part 1: Risk and Interventions," *Chronic Diseases in Canada*, 20(1): 3-13.

— (1999b) "Public Health Aspects of Breast Cancer Gene Testing in Canada Part 2: Selection for and Effects of Testing," *Chronic Diseases in Canada*, 20(1): 14-20.

Evans, R.G., M.L. Barer et al. (1994) *Why Are Some People Healthy and Others Not?: The Determinants of Health of Populations*, New York, A. de Gruyter.

Flynn, L.L. (1993) *Understanding the Role of Genetic Factors in Mental Illness*, Office of Technology Assessment Conference, Washington DC.

Fong, K.M., Y. Sekido et al. (1999) "Molecular Pathogenesis of Lung Cancer," *Journal of Thoracic and Cardiovascular Surgery*, V118(N6): 1136-1152.

Ford, D., D.F. Easton et al. (1995) "Estimates of the Gene Frequency of BRCA1 and Its Contribution to Breast and Ovarian Cancer Incidence," *American Journal of Human Genetics* 57(6): 1457-1462.

Friedman, G.D. (1987). *Primer of Epidemiology*, New York: McGraw-Hill.

Haugen, A., D. Ryberg et al. (2000) "Gene–Environment Interactions in Human Lung Cancer," *Toxicology Letters*, 112: 233-237.

Helmes, A.W., D.J.B. Karger, J. Bengal (1999) *Genetic Testing for Breast Cancer: An Issue of Money*, Report on the Second National Conference on Genetics and Public Health, Genetics and Disease Prevention: Integrating Genetics into Public Health Policy, Research, and Practice, Baltimore MD.

Holgate, S.T. (1999) "Genetic and Environmental Interaction in Allergy and Asthma," *Journal of Allergy and Clinical Immunology*, 104(6): 1139-1146.

Holgate, S.T., M.K. Church et al. (1995) "Genetic and Environmental Influences on Airway Inflammation in Asthma," *International Archives of Allergy and Immunology*, 107(1-3): 29-33.

Hubbard, R. and E. Wald (1993) *Exploding the Gene Myth: How Genetic Information Is Produced and Manipulated by Scientists, Physicians, Employers, Insurance Companies, Educators, and Law Enforcers*, Boston: Beacon Press.

Jha, P., M. Flather et al. (1995) "Antioxidant Vitamins and Cardiovascular Disease — a Critical Review of Epidemiologic and Clinical Trial Data," *Annals of Internal Medicine*, 123(11): 860-872.

Kaprio, J. (2000) "Science, Medicine, and the Future — Genetic Epidemiology," *British Medical Journal*, 320(7244): 1257-1259.

Langston, A.A., K.E. Malone et al. (1996) "BRCA1 Mutations in a Population-Based Sample of Young Women with Breast Cancer," *New England Journal of Medicine*, 334(3): 137-142.

Lauria (1992) *The Economic Impacts of Fragile X Syndrome on the State of Colorado*, Proceedings of the International Fragile X Conference, Denver, CO.

Lerman, C., B. Biesecker et al. (1997) "Controlled Trial of Pretest Education Approaches to Enhance Informed Decision Making for BRCA1 Gene Testing," *Journal of the National Cancer Institute* 89(2): 148-157.

Lock, M. (1998) "Breast Cancer: Reading the Omens," *Anthropology Today*, 14(4): 7-17.

Lynch, H.T., S.J. Lemon et al. (1997) "A Descriptive Study of BRCA1 Testing and Reactions to Disclosure of Test Results," *Cancer*, 79(11): 2219-2228.

MacMahon, B. and T.F. Pugh (1970) *Epidemiology; Principles and Methods*, Boston: Little Brown.

Malone, K.E., J.R. Daling et al. (1998) "BRCA1 Mutations and Breast Cancer in the General Population: Analyses in Women Before Age 35 Years and in Women Before Age 45 Years with First-Degree Family History," *Journal of the American Medical Association*, 279(12): 922-929.

Mapp, C.E., B. Beghe et al. (2000) "Association between HLA Genes and Susceptibility to Toluene Diisocyanate-Induced Asthma," *Clinical and Experimental Allergy*, V30(N5): 651-656.

Mattila, K.J., V.V. Valtonen et al. (1998) "Role of Infection as a Risk Factor for Arterosclerosis, Myocardial Infarction, and Stroke," *Clinical Infectious Diseases*, 26(3): 719-734.

McDermott, R. (1998) "Ethics, Epidemiology and the Thrifty Gene: Biological Determinism as a Health Hazard," *Social Science & Medicine*, V47(N9): 1189-1195.

McKinlay, J.B. and L.D. Marceau (1999) "A Tale of 3 Tails," *American Journal of Public Health*, V89(N3): 295-298.

Mitchell, A. (1997) "A Clinic to Sift Out Bad Genes," *The Globe and Mail.*

Murray, C.J.L. and A.D. Lopez (1997a) "Alternative Projections of Mortality and Disability by Cause 1990-2020: Global Burden of Disease Study," *Lancet*, 349(9064): 1498-1504.

— (1997) "Global Mortality, Disability, and the Contribution of Risk Factors: Global Burden of Disease Study," *Lancet*, V349(N9063): 1436-1442.

Neel, J.V. (1999) "Diabetes Mellitus: A 'Thrifty' Genotype Rendered Detrimental by 'Progress'?" *Bulletin of the World Health Organization*, V77(N8): 694-703.

Nussbaum, R.L., R.R. McInnes, and H.F. Willard (2001), *Thompson & Thompson Genetics in Medicine*, Philadelphia: W.B. Saunders Company, pp 242-3.

Pearce, N. (1996) "Traditional Epidemiology, Modern Epidemiology, and Public Health," *American Journal of Public Health*, V86(N5): 678-683.

— (1999) "Epidemiology as a Population Science," *International Journal of Epidemiology*, V28(N5): S1015-S1018.

Plomin, R., N.L. Pedersen et al. (1990) "Genetic Influence on Life Events During the Last Half of the Life Span," *Psychology and Aging*, 5(1): 25-30.

Ramsay, L.E. and W.W. Yeo (1991) "Hypertension and Coronary Artery Disease — An Unsolved Problem," *Journal of Cardiovascular Pharmacology*, 18(S2): S31-S34.

Reiss, D., R. Plomin et al. (1991) "Genetics and Psychiatry: An Unheralded Window on the Environment," *American Journal of Psychiatry*, 148(3): 283-91.

Rose, G. (1985). "Sick Individuals and Sick Populations," *International Journal of Epidemiology*, 14(1): 32-8.

Rothman, K.J. (1986) *Modern Epidemiology*, Boston: Little Brown.

Schottenfeld, D. and J.F. Fraumeni (1996) *Cancer Epidemiology and Prevention*, New York: Oxford University Press.

Schwab, M. (1998) *Genes and Environment in Cancer*, Berlin, New York: Springer.

Sijbrands, E.J.G., R.G.J. Westendorp et al. (2001) "Mortality Over Two Centuries in Large Pedigree with Familial Hypercholesterolaemia: Family Tree Mortality Study," *British Medical Journal*, 322(7293): 1019-1023.

Silventoinen, K., J. Kaprio et al. (2000) "Relative Effect of Genetic and Environmental Factors on Body Height: Differences Across Birth Cohorts among Finnish Men and Women," *American Journal of Public Health*, 90(4): 627-630.

Solomon, P.J., E.A. Thompson et al. (1983) "The Inheritance of Height in a Finnish Population," *Annals of Human Biology*, 10(3): 247-56.

Tambor, E.S., B.K. Rimer et al. (1997) "Genetic Testing for Breast Cancer Susceptibility: Awareness and Interest among Women in the General Population," *American Journal of Medical Genetics*, 68(1): 43-49.

Vineis, P., P. Schulte et al. (2001) "Misconceptions about the Use of Genetic Tests in Populations," *Lancet*, V357(N9257): 709-712.

Warren, S.T. and D.L. Nelson (1994) "Advances in Molecular Analysis of Fragile-X Syndrome," *Journal of the American Medical Association*, 271(7): 536-542.

Wilkinson, R.J., M. Llewelyn et al. (2000) "Influence of Vitamin D Deficiency and Vitamin D Receptor Polymorphisms on Tuberculosis among Gujarati Asians in West London: A Case-Control Study," *Lancet*, 355(9204): 618-621.

Zimmern, R.L. (1999a) "Genetic Testing: A Conceptual Exploration," *Journal of Medical Ethics*, 25(2): 151-156.

— (1999b) "The Human Genome Project: A False Dawn?" *British Medical Journal*, 319(7220): 1282-U14.

Family Physicians and Genetic Medicine: Roles and Challenges

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The rapid pace of discoveries in genetics has caught the attention of the public and health care providers. Genetics no longer deals mainly with rare disorders, but is becoming applicable to common complex diseases, such as breast and ovarian cancer, colorectal cancer, prostate cancer, heart disease, diabetes, mood disorders, Alzheimer's disease, and asthma (Guttmacher et al., 2001). Media attention to genetics and genetic testing, and direct marketing of genetic testing to health care providers and the public (Greendale and Pyeritz, 2001) have resulted in increased interest by the public (Andrykowski, et al., 1996; Graham et al., 1998). Patients are likely to ask their family physicians about genetic testing (Chalmers, et al., 2001). Family physicians are being told that genetic discoveries will change medical practice, and the future of family medicine involves determining individual genetic risk profiles, preventive care tailored to individual genetic risk, gene therapy, and choices of medications based on genetic markers to maximize effectiveness and minimize side effects (Blaine, 1999; Blaine et al., 2002).

If even some of these promises materialize, they will likely apply to the health care of the general population, as genetic factors are increasingly being found to be important in common disorders. It has been estimated that a family physician with a practice size of 2,000 would have 30 to 40 patients aged 35 to 64 who have a first-degree relative with breast, colorectal, uterine, or ovarian cancer (Johnson et al., 1995). Genetic specialists will no longer be able to satisfy the needs of the public. Referrals to genetics clinics are increasing, resulting in long waiting lists, although many of those referred are unlikely to carry mutations in known susceptibility genes (Emery and Hayflick, 2001). An Edinburgh study showed that 30 to 50 percent of patients referred to genetics services were not at significantly increased risk of developing cancer (Fry et al., 1999). Many of these low-to-moderate risk individuals could be managed by family physicians, thereby preventing delays for appointments at genetics services for genuinely high-risk patients (Fry et al., 1999).

Even if discoveries in genetics do not change medicine as dramatically as forecast, genetic tests for newly discovered gene mutations will continue to attract public interest. Increased numbers of patients with concerns or at increased genetic risk will necessitate changes to the current model of health care delivery. Increasing numbers of geneticists and genetic counsellors will likely not satisfy the escalating demands on the health system. All health care providers will need to be involved to varying degrees in genetic service delivery (Emery and Hayflick, 2001). In Canada, family physicians will need to play a role, not only in the delivery of genetic services but also in integrating genetics into their practices. Only by fully integrating genetics into primary care can we ensure access to genetic services regardless of geographic location, socio-economic status, language, and culture (Guttmacher et al., 2001).

Results of the 2001 National Family Physician Workforce Survey show that Canada lacks an adequate supply of family physicians to provide appropriate primary care services for the country's growing and changing population (CFPC, 2001). Furthermore, this survey revealed that about two thirds of the current supply of family physicians no longer accept new patients, leaving a growing number of Canadians without adequate access to primary care health services. Therefore, as the call for genetic services is anticipated to grow over time, a greater burden on existing family physician resources can be anticipated.

Family physicians see genetics as an increasingly important area of clinical medicine (Watson et al., 1999) and have expressed a willingness to play a significant role in genetic screening for common diseases (Watson et al., 1999; Suchard et al., 1999; Carroll et al., 2003). In a 1999 survey of British general practitioners, 50 percent reported counselling patients about genetic test results in the past year, and 76 percent had referred patients for genetic testing or had ordered a genetic test themselves (Suchard et al., 1999). In this study, 60 percent agreed or strongly agreed that they should be involved with genetic screening for common diseases and 64 percent were willing to take family histories and counsel patients about genetic results.

This paper examines the different roles family physicians might play in the changing world of genetic discoveries. In addition, we examine the challenges or barriers to fulfilling these roles, and existing strengths that may facilitate family physician involvement in genetic services. Last, we discuss several strategies to enable family physicians to assume these roles.

Family Physicians' Role in Genetic Services

A review of the published literature indicates that general practitioners see a role for themselves in taking a family history, assessing risk, performing a gatekeeping function, providing emotional support, and discussing the need for appropriate screening (Fry et al., 1999; Emery et al., 1999). Identification of people at low, moderate, or high risk of genetic disorders can facilitate appropriate referrals to genetics clinics (Emery and Hayflick, 2001). Many individuals at lower risk could be cared for by family physicians, freeing up appointments at genetics clinics for those at higher risk, and avoiding unnecessary anxiety about risk and testing. Family physicians are able to explore their patients' fears about their risk of genetic disorders and provide basic genetic information (Blaine et al., 2002; Carroll et al., 1999). It is known for example, that many women overestimate their risk of breast cancer, so information and reassurance may be all that is required (Pinsky et al., 2001). Because of family physicians' ongoing relationships with their patients, they are able to provide continuing support after genetic counselling and clarification of advice given to the patient by the geneticist (Blaine, 2002; Fry et al., 1999). Family physicians can help plan and implement surveillance and prevention strategies. When necessary, family physicians may refer back to genetics clinics those patients who initially tested negative, as additional family history is discovered or genetic advances become available in practice.

Some in the genomics industry have concerns that primary care providers are lacking in education about genetics and are too slow to learn about new developments in this area. They are worried that family physicians may be slow to adopt molecular diagnostic tests and thereby impede patient access to these tests (Lakhman, 2002). Others see value in the role of family physicians as "informed gatekeepers" (Caulfield, 2001), who can help patients avoid unrealistic expectations and dispel the exaggerated promises that media portray for medical genetic discoveries (Caulfield, 2001; Burke and Emery, 2002).

Challenges to Family Physicians' Involvement in the Delivery of Genetics Services

Family physicians and general practitioners face many significant challenges in adopting these potential roles in genetic service delivery in primary care. Probably the most significant is a lack of knowledge about genetics. This was highlighted in Emery's 1999 systematic review of the literature exploring the role of primary care in delivering genetics services (Emery et al., 1999). Primary care physicians accept that they have an increasing role to play in genetics, but lack confidence in their ability to do so mainly because of limited knowledge (Emery et al., 1999; Hofman et al., 1993). Many recent studies have continued to point out health providers' lack of knowledge and training in genetics (Greendale and Pyeritz, 2001; Fry et al., 1999; Watson et al., 1999; Mouchawar et al., 2001; Friedman et al., 1997; Hunter et al., 1998; Geller and Holtzman, 1991). Adequate family histories, including at least three generations, details of diagnosis, age of diagnosis and death, are not always recorded. Studies have also shown that family physicians lack adequate skills to take genetic family histories, and the family history is often used more for describing interpersonal relationships in families rather than as a genetic screening tool (Watson et al., 1999). In one study, family history was discussed during only 51 percent of visits by new patients and 22 percent of visits by established patients (Acheson et al., 2000). Fry et al. (1999) showed that the low level of understanding of cancer genetics among Scottish family physicians might lead to inappropriate referrals. Rose et al. (2001) presented general practitioners with six scenarios of family histories of breast/ovarian cancer. The percent of general practitioners making appropriate risk assessments ranged from 21 to 63 percent, and appropriate referral decisions ranged from 40 to 80 percent. On a positive note, these providers were consistent in indicating they would not refer low risk women to genetics clinics. Watson et al. (1999) showed that general practitioners did not know which patients to refer to genetics clinics or what happened in these clinics. In one of the few Canadian studies in this area (Hunter et al., 1998), the majority of physicians considered their knowledge of genetics to be adequate, but a minority were confident they could provide genetic counselling for simple genetic scenarios. Few of the Canadian physicians had used DNA diagnostic services, and most had relatively poor knowledge of what genetics services were available.

Others (Geller and Holtzman, 1991; Whittaker, 1992) have expressed concern that primary care physicians may be unable to interpret probabilistic information, may have difficulty calculating and communicating risk (Emery and Hayflick, 2001; Emery et al., 1999), may have low tolerance for uncertainty around test results (Geller and Holtzman, 1991), and may be unfamiliar with the ethical issues raised by genetic testing (Geller and Holtzman, 1991; Whittaker, 1992). In providing genetic information, physicians in general practice seem to want to focus on established genetic diseases (i.e., Down syndrome) and those diseases where there is general agreement that the test itself is reliable, and there is something useful that can be done once the results are known to minimize the risk of disability or death (Kumar and Gantley, 1999). They seem to want to continue to serve as generalists in this area and, therefore, need to have good referral guidelines and a clear idea of resources available to them and their patients, as well as information on the socio-ethical-legal and cost issues of genetic testing (Kumar and Gantley, 1999).

Another worry is that family physicians' counselling about genetics may be much more directive than that traditionally done by geneticists and genetics counsellors (Greendale and Pyeritz, 2001; Pinsky et al., 2001). Directive advice may occur more often in primary care due to time constraints imposed by the pressures of a busy clinic, because much of medical practice is by its very nature directive or because many patients expect a certain degree of directiveness from their family physicians (Greendale and Pyeritz, 2001).

Family physicians have expressed unease about the lack of evidence of efficacy for many genetic tests, particularly susceptibility testing (Mountcastle-Shah and Holtzman, 2000). In commenting on the success of the Human Genome Project, Wulfsberg (2000) felt that successful mapping did not necessarily translate into effective treatment. Family physicians may also have a healthy skepticism about the benefits of genetics in maintaining individual health and well-being. Furthermore, family physicians are uneasy discussing genetic risk unless they have an effective intervention to offer (Watson et al., 1999; Carroll et al., 2003). They understand that simply knowing genetic risk may not translate into patient lifestyle changes (Wulfsberg, 2000; Marteau and Lerman, 2001). Family physicians are also concerned about the ethical and legal implications of genetic screening, particularly confidentiality and insurance issues (Watson et al., 1999; Emery et al., 1999). Many family physicians care for multiple members of a family. Knowing the genetic test results in one family member might well affect screening decisions for other members of that family. Communication and sharing of information among family members may pose quite a challenge if family dynamics are strained. Wulfsberg (2000) commented that genetics may affect primary care delivery "in an evolutionary rather than revolutionary manner." This evolution may well prove to be a positive outcome of the "genetic revolution."

Facilitators to Family Physicians' Involvement in Genetic Services

In spite of the challenges just described, there is general support for family physicians playing a significant role in genetic service delivery (Emery et al., 1999). Some (Caroll et al., 1999) suggest that primary care providers are ideally suited to guide their patients through the decision-making process of genetic assessment and testing while at the same time addressing psychological and social issues. Such a role is indeed an extension of family physicians' well-established experience in screening and risk assessment in primary care (Kumar and Gantley, 1999). According to Guttmacher et al. (2001), the experience family physicians have in integrating the "various aspects of science and medicine into a holistic approach to patient care" will be necessary for genetics service delivery. Family medicine encompasses care at all stages of the life cycle and as such can be influenced by the full range of genetic variables (Greendale and Pyeritz, 2001; Whittaker, 1992). Genetic counselling can therefore be undertaken at the most opportune times. Family physicians have long-standing relationships with their patients. Family history can be investigated, revised, and interpreted over several visits (Greendale and Pyeritz, 2001). Because the family physician has typically known the patient for an extended period of time, counselling and support are more likely to be tailored to individual needs (Fry et al., 1999). It is not surprising that patients may seek opinions about genetic testing from their family physicians in the context of these long-term relationships. Patients have a long time frame to think about genetic information and make behaviour changes (Guttmacher et al., 2001). Perhaps family physician and patient guidelines for such advice could be developed, in collaboration with non-directive genetics specialists (Geller et al., 1993). Family physicians have a tradition of following up results with patients (Greendale and Pyeritz, 2001) and working with them to improve health behaviours. Therefore, when a patient is found to carry a predisposition gene for a disease, the family physician will tend to work with the patient to seek ways to decrease The risk of that disease (Guttmacher et al., 2001). Probably most important, the demand by their own patients for information about genetics is likely to drive family physicians to learn about genetics and stay current in this area (Greendale and Pyertiz, 2001).

How Can Family Physicians Be Helped to Integrate Genetics into Their Practices?

Most primary care providers in various studies have a favourable attitude and are ready to play a more proactive role in genetic counselling and testing, but are clear that they lack knowledge and need targeted educational programs (Escher and Sappino, 2000). Those who would counsel about genetics or refer to genetics services are more likely to have greater knowledge of genetics, greater confidence in communicating with their patients about genetics, and higher tolerance for ambiguity (Geller et al., 1993).

What is needed for family physicians to integrate genetics into their practices? More effective and efficient methods for obtaining and updating family histories need to be devised and evaluated (Greendale and Pyeritz, 2001). Although currently limited in number, computerized approaches are being developed and evaluated (Greendale and Pyeritz, 2001; Emery et al., 2000; Ashbury and Polzer, 2001). One such tool, the Risk Assessment in Genetics (RAGs), is a computer program to support primary care providers recording and interpreting family histories of breast and ovarian cancer patients (Emery et al., 2000). A beta version of a CD-ROM designed to improve physicians' knowledge of genetics, and for which they can receive continuing education credits by successfully completing the course on the tool, is being circulated to US physicians for evaluation (Ashbury and Polzer, 2001). A comparatively larger number of Web-based tools are available through the Internet, developed by private interests, genetic services programs, universities, professional groups, and not-for-profit organizations (Ashbury and Polzer, 2001). Many of these are directed at both the public and health care providers, and have a disease-specific focus. Web based resources in genetics in England and the United States have recently been reviewed (Stewart et al., 2001; Pagon et al., 2001). In Ontario, work is ongoing to develop OnGene, the Ontario Genetics Services Resource Site. The OnGene site <http://www.ongene.ca>, will provide access to information on genetic services and genetic tests (cytogenetic, molecular, and prenatal) available for patient care in Ontario. The site will contain information about genetic tests and services available at accredited test centres in Ontario, key educational information about common genetic diseases, including how and when to offer testing, and links to other sites. Family physicians can also access educational information through the Mount Sinai Hospital Family Medicine Genetics Web site: <http://www.mtsinai.on.ca/familymedicine/genetics>. Only some Web-based tools pertaining to genetics and genetics education were developed solely for family physicians (Ashbury and Polzer, 2001). Formative evaluation strategies have dominated the assessment of these tools, thereby limiting our understanding of the potential impact of these educational interventions on practitioners' knowledge, attitudes, skills, or practices regarding the delivery of genetic services (Ashbury and Polzer, 2001).

Genetics referral guidelines have been shown to help general practitioners make more appropriate referrals (Lucassen et al., 2001). Watson et al. (2001) developed an information pack on familial breast/ovarian cancer containing a laminated summary card with simple referral guidelines, a booklet with more detailed background information and two patient leaflets. They randomized practices to a group who received an information pack plus an in-practice educational session, a group that received the information pack alone and a group that received neither. The main outcome was the proportion of general practitioners making the correct referral decision on at least five out of six family history vignettes. They found that providing general practitioners with this information pack significantly improved referral decisions regarding patients with a family history of breast/ovarian cancer. The in-house educational session was extremely well received, but produced no additional improvements in performance. Those who received the educational session plus information pack reported greater confidence in managing this type of genetic problem. In another study, a one-session genetics educational program for primary care providers was used to assess knowledge and attitudes using a pre- and post-intervention design. Pretest assessment revealed less than adequate knowledge about basic genetic principles and relatively positive attitudes among the subjects (Kolb et al., 1999). They were able to show significant increases in knowledge about genetic conditions and attitudes toward provision of genetic services.

Guidelines for referral to genetics clinics might be computer-based. Electronic rules would be built into the computer application to identify only those individuals who are eligible for testing and interventions (Watson et al., 1999).

Training in risk communication is frequently recommended. However, there are few studies suggesting how this training might be accomplished in primary care (Watson et al., 1999).

Many have recommended that specialist genetics services be more closely linked with primary care (Watson et al., 1999). These linkages might be through community genetics clinics (Fry et al., 1999) or genetic counsellors acting as outreach workers, liaising with general practitioners (Emery and Hayflick, 2001).

Patient information aids have been suggested as a method for educating the public and enabling them to stratify their own risk of genetic disease (e.g., hereditary cancers), thus facilitating informed choice. Such an aid is the Hereditary Breast Cancer Information Aid, which was rated as excellent or very good by 91 percent of participants (Warner et al., 2003). In family practices in Ontario, it demonstrated significant improvement in knowledge with no increase in breast cancer worry (Warner et al., 2003). The aid is available through the Canadian Cancer Society Web site: <http://wwwhereditarybreastcancer.cancer.ca>. A similar information aid for hereditary colorectal cancer is being developed and evaluated through a grant from the Canadian Institutes of Health Research (CIHR) (McLaughlin et al., 2001). Iverson et al. (1998) concluded that "strategies that are directed at physicians and patients simultaneously are likely to have the most immediate and the greatest effect [on physician practice behaviours]."

Emery and colleagues have stated that what is needed for primary care physicians to integrate genetics into practice includes referral guidelines, computerized risk assessment, skills in assessment and communication of risk, management guidelines, and local genetics clinics as resources (Emery and Hayflick, 2001; Emery et al., 1999). They consider the possibility of the development of the "primary care genetics specialist" who might act as an intermediate referral resource. Emery et al. also suggest that a general practitioner in each group practice might be trained in genetics skills to act as an in-house expert, supported by electronic resources (Emery and Hayflick, 2001). This model may not work in Canada, because of the geographic distance of some practices and the existence of much smaller group practices, although telemedicine might ameliorate these challenges. Also, the model is not compatible with the idea of fully integrating genetics into all primary care providers' skill set. In addition, Emery et al. stress the need for undergraduate education in genetics and promotion of an integrated approach to genetic medicine at all medical education venues (Emery and Hayflick, 2001; Emery et al., 1999). Younger physicians who received some genetics in their preclinical and clinical training have been shown to have a higher level of comfort with providing genetic advice than those who graduated in the more distant past (Hofman et al., 1993). A key strategy to facilitate family physician participation in genetic services is to ensure appropriate education at the undergraduate level and continuing education programs. Burke and Emery (2002), in an excellent recent article in *Nature*, also stress the need for a problem-based medical school curriculum in genetics, continuing medical education for practising physicians in genetics and innovative approaches for delivering genetic information to practitioners (Burke and Emery, 2002).

Two interesting educational projects in genetics are ongoing in the United States. In 1996, the National Coalition for Health Professional Education in Genetics (NCHPEG) was established. This interdisciplinary organization is devoted to health professional education in genetics (Guttmacher et al., 2001; Kenner, 1998). NCHPEG has developed core competencies (see <www.nchpeg.org>) in genetics for health professionals. It has also established the Genetics in Primary Care Project, the goal of which is to enhance the ability of faculty to incorporate clinical application of genetic information into undergraduate and graduate primary care medical education (Greendale and Pyeritz, 2001). This project consists of a case-based curriculum and educational interventions, such as workshops, lectures, and interactive case discussions by genetics/primary care teams in 20 participating institutions (Burke and Emery, 2002). NCHPEG also identified areas of controversy, such as indications for referral and non-directive counselling, and have promoted dialogue in these areas. This program is being evaluated.

In Canada, interest among family physicians about genetics is just beginning (Carroll et al., 2003), and requests for continuing education in genetics are increasing. A practice-based learning module entitled "Genetic Screening for Hereditary Breast/Ovarian and Colorectal Cancers" (Blaine and Carroll, 2002) has been published by The Foundation for Medical Practice Education in partnership with Health Canada. It is being used by family physicians in Canada in small group learning situations. Several federal and provincial committees have also been working on educational strategies for primary care providers and the public in the area of genetics.

Conclusion

Caulfield (1999), while agreeing that genetics may be the future of medicine, has questioned whether family physicians will be adequately prepared to deliver genetics services. He anticipates that physicians will face many patient inquiries, commercial marketing, and malpractice claims, for which they may not be prepared. He stresses that "medical schools, family physicians, medical geneticists and other genetic professionals need to work together to ensure that Canadian physicians have the knowledge base necessary to thoughtfully consider emerging policies and to help patients make informed decisions about gene testing." Family physicians have an increasing role to play in the provision of genetics services, and this role needs to be integrated into existing genetics service delivery initiatives. Patients are likely to seek the involvement of their family physicians as genetics makes headway into the more common diseases. At the same time, there are challenges, including resource constraints, family physicians' knowledge and attitudes toward genetic discoveries, and communicating with patients about genetics. To optimize their role, family physicians require information and skills training in genetics service delivery, resources to facilitate patient education and clinical practice guidelines to facilitate risk assessment and management. Training should be provided at the undergraduate level, and continuing education programs must be accessible for physicians in practice. However, there is a dearth of genetic education tools for family physicians and comparatively few of the existing tools have been evaluated, leaving little guidance on what tools are needed, the format and content of these tools to optimize physician and patient education, or how the tools should be used in practice. As primary care becomes a more common point of entry by which people are made aware of and referred for genetic assessment, family physicians must be educated regarding the types of concerns and questions their patients may have, including the psychosocial issues of testing. Primary care providers have expressed a willingness to play a significant role in the delivery of genetics services, but these education and practice challenges must be addressed.

References

Acheson, L.S., G.L. Wiesner, S.J. Zyzanski, M.A. Goodwin, and K.C. Stange (2000) "Family History-Taking in Community Family Practice: Implications for Genetic Screening," *Genetics in Medicine*, 2(3): 180-185.

Andrykowski, M.A., R.K. Munn, and J.L. Studts (1996) "Interest in Learning of Personal Genetic Risk for Cancer: A General Population Survey," *Preventive Medicine*, 25: 527-36.

Ashbury, F., and J. Polzer (PICEPS Consultants, Inc.) (2001) *Educational Tools Which Relate to Adult-Onset Disorders for Which Genetic Testing Is Available*, Final report prepared for the Working Group on Public and Professional Educational Requirements Related to Genetic Testing of Late Onset Disease, Health Canada, August. Available at: <http://www.hc-sc.gc.ca/pphb-dgspsp/ publicat/genetics/>.

Blaine, S. (1999) "The Genetics Revolution — Implications for Family Physicians and Their Patients," *Patient Care*, 10(4): 46-66.

Blaine, S. and J.C. Carroll (2002) "Genetic Screening for Hereditary Breast/Ovarian and Colorectal Cancers," *The Foundation for Medical Practice Education*, 10(6): 1-9.

Blaine, S., J.C. Carroll, and M.J. Esplen (2002) "Managing Patients with a Family History of Cancer: Psychosocial Issues and the Evolving Role of the Primary Care Physician," *Primary Psychiatry*, 9(5): 34-38.

Burke, W., and J. Emery (2002) "Genetics Education for Primary-Care Providers," *Nature*, Reviews/Genetics, 3: 561-566.

Carroll, J.C., R.E. Heisey, E. Warner, V. Goel, and D.R. McCready (1999) "Hereditary Breast Cancer: Psychosocial Issues and Family Physicians' Role," *Canadian Family Physician*, 45: 126-132.

Carroll, J.C., J.B. Brown, S. Blaine, G. Glendon, P. Pugh, and W. Medved (2003) "Genetic Susceptibility to Cancer: Family Physicians' Experience," *Canadian Family Physician*, 49: 45-52.

Caulfield, T. (1999) "Gene Testing in the Biotech Century: Are Physicians Ready?" *Canadian Medical Association Journal*, 161: 1122-4.

— (2001) "The Informed Gatekeeper?: A Commentary on Genetic Tests, Marketing Pressure and the Role of Primary Care Physicians," *Health Law Review*, 9(3): 14-18.

CFPC (College of Family Physicians of Canada) (2001) "Not Enough Family Physicians to Meet Patient Needs: Results of the 2001 National Family Physician Workforce Survey," News release. Available at: <http://www.cfpc.ca/communications/newsreleases/nr25october2001.asp>.

Chalmers, K.I., K.A. Luker, S.J. Leinster, I. Ellis, and K. Booth (2001) "Information and Support Needs of Women with Primary Relatives with Breast Cancer: Development of the Information and Support Needs Questionnaire," *Journal of Advanced Nursing*, 35(4): 497-507.

Emery, J. and S. Hayflick (2001) "The Challenge of Integrating Genetic Medicine into Primary Care," *British Medical Journal*, 322: 1027-30.

Emery, J., E. Watson, P. Rose, and A. Andermann (1999) "A Systematic Review of the Literature Exploring the Role of Primary Care in Genetic Services," *Family Practice*, 16: 426-445.

Emery, J., R. Walton, M. Murphy, J. Austoker, P. Yudkin, C. Chapman, A. Coulson, D. Glasspool, and F. Fox (2000) "Computer Support for Interpreting Family Histories of Breast and Ovarian Cancer in Primary Care: Comparative Study with Simulated Cases," *British Medical Journal*, 321: 28-32.

Escher, M. and A.P. Sappino (2000) "Primary Care Physicians' Knowledge and Attitudes Towards Genetic Testing for Breast/Ovarian Cancer Predisposition," *Annals of Oncology*, 11(9): 1131-5.

Friedman, L.C., S.E. Plon, H.P. Cooper, and A.D. Weinberg (1997) Cancer Genetics Survey of Primary Care Physicians' Attitudes and Practices," *Journal of Cancer Education*, 12: 199-203.

Fry, A., H. Campbell, H. Gudmundsdottir, R. Rush, M. Porteous, D. Gorman, and A. Cull (1999) "GPs' Views on Their Role in Cancer Genetics Services and Current Practice," *Family Practice*, 16: 468-474.

Geller, G. and N.A. Holtzman (1991) "Implications of the Human Genome Initiative for the Primary Care Physician," *Bioethics*, 5(4): 318-325.

Geller, G., E.S. Tambour, G.A. Chase, K.J. Hofman, R.R. Faden, and N.A. Holtzman (1993) "Incorporation of Genetics in Primary Care Practice — Will Physicians Do the Counseling and Will They Be Directive?" *Archives of Family Medicine*, 2: 1119-1125.

Graham, I.D., D.M. Logan, R. Hughes-Benzie, W.K. Evans, H. Perras, L.M. McAuley, A. Laupacis, and H. Stern (1998) "How Interested Is the Public in Genetic Testing for Colon Cancer Susceptibility? Report of a Cross-Sectional Population Survey," *Cancer Prevention & Control*, 2: 167-72.

Greendale, K, and R.E. Pyeritz (2001) "Empowering Primary Care Health Professionals in Medical Genetics: How Soon? How Fast? How Far?" *American Journal of Medical Genetics*, 106(3): 223-32.

Guttmacher, A.E., J. Jenkins, and W.R. Uhlmann (2001) "Genomic Medicine: Who Will Practice It? A Call to Open Arms," *American Journal of Medical Genetics* (Semin. Med. Genet.), 106: 216-222.

Hofman, K.J., E.S. Tambor, G.A. Chase, G. Geller, R.R. Faden, and N.A. Holtzman (1993) "Physicians' Knowledge of Genetics and Genetic Tests," *Academic Medicine*, 68(8): 625-632.

Hunter, A, P. Wright, M. Cappelli, A. Kasaboske, and L. Surh (1998) "Physician Knowledge and Attitudes Towards Molecular Genetic (DNA) Testing of Their Patients," *Clinical Genetics*, 53: 447-455.

Iverson, D.C., F.D. Ashbury, and E.A. Clarke (1998) "A Literature Review to Identify Principles to Facilitate Physician Behaviour Change to Adopt and Implement Clinical Practice Guidelines." Report prepared for the Adult Health Division, Health Canada.

Johnson, N., T. Lancaster, A. Fuller, and S.V. Hodgson (1995) The Prevalence of a Family History of Cancer in General Practice," *Family Practice*, 12: 287-289.

Kenner, C. (1998) "National Coalition for Health Professional Education in Genetics," (American Association of Critical-Care Nurses) *ACCN Clinical Issues*, 9(4): 582-587.

Kolb, S.E., M.C. Aguilar, M. Dinenberg, and C.I. Kaye (1999) "Genetics Education for Primary Care Providers in Community Health Settings," *Journal of Community Health*, 24(1): 45-59.

Kumar, S. and M. Gantley (1999) "Tensions Between Policy Makers and General Practitioners in Implementing New Genetics: Grounded Theory Interview Study," *British Medical Journal*, 319: 1410-13.

Lakhman, K. (2002) "Unenlightened General Physicians May Hinder Nascent Molecular-Diagnostics Market," *GenomeWeb News*, New York: May 8. <www.genomeweb.com/articles/view-article.asp?Article=200258145855>.

Lucassen, A., E. Watson, J. Harcourt, P. Rose, and J. O'Grady (2001) "Guidelines for Referral to a Regional Genetics Service: GPs Respond by Referring More Appropriate Cases," *Family Practice*, 18: 135-140.

Marteau, T.M. and C. Lerman (2001) "Genetic Risk and Behavioural Change," *British Medical Journal*, 322:1056-9.

McLaughlin, J., J.C. Carroll, S. Blaine, G. Worrall et al. (2001) Interdisciplinary Research on the Determinants, Impact and Control of Colorectal Cancer — A Genetic-Epidemiological and Population-Based Approach, Canadian Institutes of Health Research IHRT grant. Awarded January 2001.

Mouchawar, J., C.E. Klein, and L. Mullineaux (2001) "Colorado Family Physicians' Knowledge of Hereditary Breast Cancer and Related Practice," *Journal of Cancer Education*, 16: 33-37.

Mountcastle-Shah, E. and N.A. Holtzman (2000) "Primary Care Physicians' Perceptions of Barriers to Genetic Testing and Their Willingness to Participate in Research," *American Journal of Medical Genetics*, 94: 409-416.

Pagon, R.A., L. Pinsky, and C.C. Beahler (2001) "Online Medical Genetics Resources: A US Perspective," *British Medical Journal*, 322: 1035-7.

Pinsky, L.E., J.B. Culver, J. Hull, E. Levy-Lahad, M. Daly, and W. Burke (2001) "Why Should Primary Care Physicians Know about Breast Cancer Genetics?" *Western Journal of Medicine*, 175: 168-173.

Rose, P.W., E. Watson, P. Yudkin, J. Emery, M. Murphy, A. Fuller, and A. Lucassen (2001) "Referral of Patients with a Family History of Breast/Ovarian Cancer — GPs' Knowledge and Expectations," *Family Practice*, 18: 487-490.

Stewart, A., N. Haites, and P. Rose (2001) "Online Medical Genetic Resources: A UK Perspective," *British Medical Journal*, 322: 1037-1039.

Suchard, M.A., P. Yudkin, J.S. Sinsheimer, and G.H. Fowler (1999) "General Practitioners' Views on Genetic Screening for Common Diseases," *British Journal of General Practice*, 49: 45-46.

Warner, E., J.C. Carroll, R.E. Heisey, V. Goel, W.S. Meschino, H.L.A. Lickley, B.D. Doan, P. Chart. V. Orr, and S. Lothian (2003) "Educating Women About Breast Cancer: An Intervention for Women with a Family History of Breast Cancer," *Canadian Family Physician*, 49: 56-63.

Watson, E.K., D. Shickle, N. Qureshi, J. Emery, and J. Austoker (1999) "The 'New Genetics' and Primary Care: GPs' Views on Their Role and Their Educational Needs," *Family Practice*, 16: 420-425.

Watson, E., A. Clements, P. Yudkin, P. Rose, C. Bukach, J. Mackay, A. Lucassen, and J. Austoker (2001) "Evaluation of the Impact of Two Educational Interventions on GP Management of Familial Breast/Ovarian Cancer Cases: A Cluster Randomised Controlled Trial," *British Journal of General Practice*, 51: 817-821.

Whittaker, L.A. (1992) "The Implications of the Human Genome Project for Family Practice," *Journal of Family Practice*, 35: 294-310.

Wulfsberg, E.A. (2000) "The Impact of Genetic Testing on Primary Care: Where's the Beef?" *American Academy of Family Physicians*, 61: 971-8.

Privacy and Property? Multi-Level Strategies for Protecting Personal Interests in Genetic Material

Graeme Laurie

This paper builds on my earlier work, which examined privacy issues as they relate to genetic material and information derived from that material.[1] In that work, I argued that a more robust concept of privacy is required than is currently available to allow us to meet challenges posed by the increased availability of genetic information. I argued that existing medico-legal paradigms, such as respect for individual autonomy and protection of patient confidentiality, do not provide adequate protection for the range of interests individuals might have in their genetic constitution.

Accordingly, I have proposed a new model of privacy protection that seeks to complete the family of values that I believe should work in parallel to provide such protection. However, although I am generally "pro-privacy," I also recognize the limitations of privacy, both in theory and in practice. One such limitation is that a privacy right — however conceived — is always a right of non-interference. It does not constitute a right of positive entitlement. To this extent, privacy suffers from limitations similar to those that afflict the principle of respect for autonomy; namely, it does not provide for any *continuing control* over personal matters once they enter the public sphere. Autonomy in the guise of consent reduces control to the giving or withholding of that consent after which an individual is largely powerless to dictate what happens.[2]

Thus, for example, while an individual might consent to make private information public, the individual will have no continuing control over what is then done with the data. Similarly, if an individual consents to provide tissue samples for research purposes he/she loses control of those samples for all time coming. The individual is not in a position to dictate the fate of the samples by exercising her/his right to privacy. And, while privacy of any information derived from those samples may continue to be protected, any residual authority depends on the nature of the original consent and, more important, on the assumption that its terms will not be violated. Privacy and autonomy are, therefore, of limited utility in this respect.

They are, however, unified at the fundamental level by the fact that each reflects a valued aspect of the human personality.[3] If, however, we find them inadequate guardians of "self," we should explore other options — as yet largely uncharted — that may give fuller protection to interests in the persona. German law, for example, protects the body as an aspect of the right to personality. So, if interference occurs with excised parts of the body, such as the unauthorized destruction of sperm, the law will provide a remedy for a breach of the *Persönlichkeitsrecht* (Bundesgerichtshof, 1993). The way this is done is by recognizing enforceable property rights in excised human material.[4]

Anglo-American law is less sophisticated in this regard. Our tendency has been to treat privacy and autonomy as one branch of protection, and property as another. Numerous examples of this can be given. Most notable is the experience in Oregon, where the state took the bold step in 1995 of embodying a personal property right in genetic information and DNA samples when used for anonymous research with the result that unauthorized interference with either constituted a tort actionable at law.[5] However, after several years of lobbying by the pharmaceutical industry and research institutes, a new bill was passed in June 2001 that removed this right and replaced it with more stringent privacy protection.[6] The claim is that Oregon will now have the most far-reaching privacy legislation of its kind in the United States. The reality is that the two concepts of privacy and property are treated as either/or options when there is no sound reason to do so. The Oregon experiment was not given sufficient time for the promise and the pitfalls of a property paradigm to be explored and addressed.

In the United Kingdom, the Human Genetics Commission (HGC, 2002) recently issued its recommendations on protecting personal genetic data, but it too has eschewed the property paradigm in favour of an approach couched in the traditional concepts of "more and better consent" and "adequate protection of privacy interests."[7] This would not be so objectionable but for the fact that property rights *are* granted over human material. This happens all the time, and is actively encouraged by governments around the world. It happens, of course, through the mechanisms of intellectual property law, and primarily through the granting of patents. But the property owners in such cases, as the infamous *Moore* case demonstrated only too well,[8] are the "inventors" (i.e., the researchers), and not the subjects from whom the material was derived. Much has been written about the inequities of this, and it has even prompted the Human Genome Organisation's Ethics Committee (HUGO, 2000a), admirably, to recommend that "profit-making entities dedicate a percentage (e.g. 1-3%) of their annual net profit to healthcare infrastructure and/or to humanitarian efforts." However, in this short paper I would like to propose an alternative strategy, namely, recognition of property rights in ourselves.

The Need for an Additional Approach?

One might ask why such a strategy is needed? A number of points can be made. There is, for example, an undeniable public crisis of confidence in genetic research, even though its promise is well recognized. This is borne out by the UK Medical Research Council (MRC)'s survey into public perceptions of the collection of human biological samples — published in October 2000.[illegible] This general atmosphere of mistrust is compounded in large part by the increased role the private sector has assumed in undertaking, financing, and staking a claim to research involving human genetic material. The granting of intellectual property rights over the products of this research has served only to alienate the public even further. These issues will not be addressed adequately by simply removing intellectual property protection from the equation. Pragmatically, this is not even a viable option but, more important, the very strong public interest in encouraging innovation would be lost to any state or geographical area that attempted to use it. The research and innovation that biotechnology attracts would simply move elsewhere. The real problem is twofold. First, where should the proper focus lie in addressing this crisis of confidence? Second, what role, if any, should law play in that process?

The reality is that those who participate as subjects and who provide vital genetic research material are the key components of the genetic research machine and are crucial to its continued success. Whether represented by individuals or communities, they are undervalued, under respected and undermined. The way forward is to empower these parties to take a more equal role in the partnership that is formed when they participate in research (Greely, 1998). The starting point is to break free of current institutional constraints that stand in the way of this progress and explore more imaginative ways to establish, and perhaps protect, the role of those who further the *public* interest in genetic research.

Maybe so, but why property? Well, many who advocate a more consistent application of the law have strongly objected to the exclusion of individuals from the human property model, when this model is available to others.[10] This, in turn, is part of a wider movement that involves a re-assessment of the relationship individuals enjoy with their own bodies and the legal rights that can be claimed in respect of that relationship.[11]

Moreover, current models are inadequate to redress imbalances. The conflation of autonomy with consent that is typical of current approaches to medico-legal dilemmas reduces the means of respecting individuals to one solitary event — obtaining informed consent. And, while numerous ways of maintaining respect for individuals are available when they remain passive in the process,[12] the equiparation of autonomy with consent means that informed consent has come to be the primary, and arguably the only, legitimate way of *empowering* individuals in their dealings with health care professionals and researchers. This is also true in the spheres of intellectual property and biotechnology. But this need not and should not be so. Two examples illustrate the current approach.

When the European Patent Office's Opposition Division was called upon in 1994 to examine the morality of Howard Florey's patent over H2-Relaxin — a protein secreted by pregnant woman that eases the process of childbirth — it did so in large part by reference to the principle of informed consent.[13] It had been objected, inter alia, that the granting of the patent offended morality, because it required the removal of tissue from pregnant women. This was said to be an affront to human dignity, because it used a particular female condition (pregnancy) for a technical process oriented toward profit. The answer of the Opposition Division, however, was that the tissue had been freely donated by the women in question and, therefore, the manipulation of genetic material from those samples was not immoral.[14]

Second, Recital 26 of the European Directive on the legal protection of biotechnological inventions provides that:

> Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law.[15]

The terms of Recital 26 were originally intended for inclusion as an article of the Directive with clear binding force on member states. But, heavy lobbying by representatives of the biotechnology and patent industries meant it was ultimately relegated to the preamble to the Directive, where its legal status and its effect on member states is far less certain.[16]

Such formulations of consent certainly provide adequate protection for the researchers. They also represent one means of respecting individuals. Indeed, they are highly desirable safeguards. However, they are considerably less successful as a means of empowering individuals. But, it might be asked, why would we be concerned to empower individuals anyway? Well, it is precisely because people feel disenfranchised from, and disempowered by, the modern machinery of research that we face the current public crisis of confidence in research in general and genetic research in particular. Individuals who provide samples for research purposes are not, and do not feel like, stakeholders in the enterprise. The continued participation and support of the public in research activity can only be ensured by a fundamental reappraisal of the relationships with the subjects that have traditionally been accepted.

The imperative to seek and obtain consent from research subjects gives them an illusion of power and control. In reality, it delegates extremely limited control to individuals. The sole power that is afforded is that to withhold consent (i.e., to refuse). Moreover, there is no residual power once consent has been given unless further consent is required at some future point. This is demonstrated particularly well in the context of the donation of samples for research. While no individual will be forced to give samples — and in most cases the only ethically and legally appropriate approach is to seek informed consent to the provision of a sample — the individual retains no continued relationship with the sample in either a factual or a legal sense once consent has been obtained and the sample surrendered. Thus, the focus on consent renders the participatory process disempowering in at least two senses. For those who genuinely wish to participate in research, the availability of a "right to refuse" is useless, and the one-off event of consent is disempowering, because it fails to recognize the individual subject or, indeed, the community of research subjects, as a party with an interest in the overall endeavour. In sum, the fundamental problem with the consent model is that it does not provide a means by which the subjects can exercise *continuing control* of her/his materials.[17]

Revisiting the Gift Model

This problem is compounded by the continuing use of the gift model that has traditionally served to govern the researcher–subject relationship. The notion of gift has a strong normative appeal in lay terms, not least because it is seen to be a laudable act, demonstrating the virtues of altruism and beneficence, and untainted by the twin evils of self-interest or exploitation. In practice, it has considerable utility for the recipient, in that gifts, for research purposes are treated as unconditional. This provides broad scope for the future use or disposal of the gift. As to public interest, unconditional gifting can serve a number of valuable social ends, including advances in medical research and the development of therapeutic agents or cures. This particular consideration weighs heavily as an unquestionable given, to which we shall return presently. But such a concept of gift is seriously incongruous in legal terms. In English law, "gift" is defined as "the transfer of any *property* from one person to another gratuitously" (Halsbury's, nd, emphasis added).

Thus, in legal terms the invocation of *gift* presupposes underlying property rights in the subject matter that constitutes the gift. As a result, the legal position in respect of ownership of donated human body parts is in disarray in most western legal systems.[18] A fair summation is that while there is no clear prohibition on ownership of body parts — and indeed, one can find many examples of a property model being applied to human tissues — the one player who is routinely excluded from the property model is the source of the property itself.[19]

The classic policy decision on self-ownership is to be found in the decision of the Supreme Court of California in *Moore v. Regents of the University of California*,[20] in which the Supreme Court of California denied the plaintiff any legal recognition of property rights in his own excised spleen cells. The court held that because no precedent could be found on which to ground Moore's property claim, and because of the utilitarian consideration that a finding for the plaintiff would be a hindrance to medical research "by restricting access to the necessary raw materials,"[21] it was inappropriate to recognize individual property rights in the body. Moreover, the Court was concerned that a contrary decision would "[threaten] to destroy the economic incentive to conduct important medical research" because "[i]f the use of cells in research is a conversion, then with every cell sample a researcher purchases a ticket in a litigation lottery."[22] The paradox in this decision was highlighted by the dissent of Broussard, J. wherein he stated:

> ...the majority's analysis cannot rest on the broad proposition that a removed part is not property, but rather rests on the proposition that a *patient* retains no ownership interest in a body part once the body part has been removed from his or her body.[23]

Does it remain reasonable or defensible to exclude completely from the equation the one person who can make everything possible?

More particularly, it is interesting to note how the court in *Moore* seemed entirely satisfied that its adoption of the consent model was sufficient to provide respect for, and to empower, the plaintiff (for Moore won in respect of lack of informed consent). The consent model and the property model were treated as though they were mutually exclusive — a phenomenon that has also been noted above in respect of property and privacy. There is, however, no sound reason why this should be so.

A Property Paradigm

It is undeniable that an attitudinal shift is occurring in respect of the way we regard our bodies and any parts removed from them. The recent MRC survey on the perceptions of the public on the collection and use of human biological samples found that younger people tended to view payment for excised bodily tissues as a matter of right or at least as a logical and acceptable option (MRC, 2000). This was especially so when research was undertaken for profit by private enterprises. In corroboration, the Human Genetic Commission's poll (2001: 27-28) found considerable antipathy to the idea of exclusive ownership of genetic information by research organizations. Contrariwise, members of the older generation found more comfort in the classic gift paradigm, expecting nothing in return for altruistic and public spirited donations (HGC, 2001, para 6.12). And yet, many general practitioners and nurses who took part in the survey also supported the view that volunteers should retain a degree of ownership in donated samples (HGC, 2001, para. 17). Indeed, the MRC Working Group on Human Tissue and Biological Samples for Use in Research opined: "[I]t was more practical and more attractive from a moral and ethical standpoint to adopt the position that, if a tissue sample could be property, the original owner was the individual from whom it was taken" (MRC, 2001, para. 2.2.1).

It is submitted that there is nothing in principle to prevent recognition of property interests in aspects of the self, subject of course to limitations against self-harm. A personal property paradigm could, in fact, serve an all-important role in completing the picture of adequate protection for the personality in tandem with other protections such as autonomy, confidentiality, and privacy (Moore, 2000). However, the added value of a property model lies in its ability to empower individuals and communities, and to provide the crucial continuing control over samples or information through which ongoing moral and legal influence may be exerted.

Property implies many things, including ownership and control. Property protection is, however, by no means an absolute and, as with all of our other legal rights, property rights can be tempered in our own interests or in those of others. Exercises of self-ownership therefore need not be recognized if these conflict with an individual's best interests. Examples include attempts to dispose of vital organs or tissues that would be detrimental to health. Nor should the law ever condone ownership of entire living, breathing human beings as this would be a fortiori impermissible as slavery. Nonetheless, the recognition of property rights in excised body parts or samples does not carry any of these risks.

The way that the concept of gift has been used in research culture presumes surrender of all residual interests in donated samples. However, not only does this lack support in law but it has also prompted the dual disservices of justifying a distorted gift paradigm while fuelling inconsistencies that ultimately undermine public confidence in research (Mason and Laurie, 2001).

It is no longer clear that the model of gifting currently employed in the modern research environment remains appropriate. It is not true, for example, that individuals retain no interest in materials surrendered for research. The moral significance of body parts remains even when they are separated from their original source. The MRC (2000, para. 6.9) has found, for example, that "[v]irtually everyone said that if they donated a sample they would appreciate feedback on what the research using their samples had discovered or achieved."

Nor should we ignore the fact that the commercial value that human material might represent to researchers also represents a potential value in those terms to the sample sources themselves. Not everyone agrees with the Supreme Court of California in *Moore* (Lin, 1996). Numerous commentators point to principles of fundamental equity, the redress of unjust enrichment, and the protection of personal interests that can be furthered through property rights.[24]

The recognition of this kind of interest in personal samples would provide the continuing control that is so lacking under the consent model alone (Seeney, 1998). Meaningful, legally relevant and enforceable conditions could be placed on any transfer of the property and so ensure that a research participant or indeed a community retains a vested interest in samples and in the goals and outcomes of any research for which those samples are provided. By the same token, restrictions on the inclusion of undesirable clauses by either side could easily be imposed by law.[25] It might be objected, for example, that property rights could easily be waived under pressure. The obvious retort to this is that no such assignation of rights should be legally permissible. Thus, while individuals or communities might choose not to exercise their rights, they cannot give them away.

Current Movements Toward a Property Model

Examples of communities working together can be found in North America where families have used their genetic uniqueness as a bargaining tool. Those suffering from the rare genetic disorder Pseudoxanthoma elasticum (PXE) have reached agreement with researchers to provide samples only on the condition that they are named as joint patentees in any subsequent patent applications, with a right to 50 percent of any proceeds.[26] This is an interesting reversal of fortune, for historically researchers would not take samples unless the consent included a grant of full title, even if this was meaningless in law. That such a bargain has been struck signals an important change in research culture, although the point remains that the property interests claimed by the families and their representatives may be unfounded in law. Fundamental principles of justice certainly support this approach (HUGO, 2000b), but whether it could withstand serious legal analysis is open to debate (Knoppers, 2000). More such arrangements will undoubtedly be made.

The reader should not take away from this discussion an impression that the property model being advocated amounts only to some crude instrument requiring that research subjects be paid for their trouble. Rather, it is offered as a vehicle for further discussion and analysis of certain crucial elements that must be strengthened to advance the public interest in genetic research. A cultural shift in attitude must occur, as must a reassessment of the nature of the relationship between researchers and subjects. These can be achieved, in part, through the discourse of property.

The language we use predisposes us to certain attitudes toward each other and serves to establish the nature and the limits of any claims we might make of each other. The law has the power to legitimize some of these claims by giving them the status of enforceable rights. We ought, then, to consider what it would mean to talk in terms of property rights in ourselves and how that language might be translated into law.

At the time of writing, a seminal case is proceeding through the American courts brought by parents of children affected by Canavan disease against researchers who developed and patented a test for the disorder using samples donated by the families.[illegible] The defendants had worked closely with afflicted families receiving samples and gaining access to registers containing details of other affected groups around the world. However, when the Canavan gene was eventually identified the researchers sought a patent over it and a related test, and proceeded to restrict access to the latter save through tightly controlled exclusive licences. The plaintiffs objected strongly and have mounted an action on a number of grounds. These include lack of informed consent, breach of fiduciary duty, and conversion. In this last respect, the plaintiffs claim a property interest in their samples, the genetic information therein, and information contained in the Canavan Registry.

Paradoxically, this case stands in stark contrast to *Moore*. Here, policy favours the plaintiffs. The families want information about the disease and the test to be freely available while it is the patent holders who wish to restrict access and so potentially hinder research. Policy will undoubtedly have a significant role to play in the outcome, but the policy arguments are strong on both sides,[illegible] and attitudes have moved on since *Moore* was decided in 1990.[illegible]

Defending a Property Model

A number of counter-arguments can, however, be mounted. The concern that property rights in the self will hinder research held sway in *Moore* and lies at the core of the amendments to the Oregon law. However, it is far from established fact that research will be obstructed by giving sample sources some small measure of bargaining power. Indeed, in the scheme of relative powers, those who provide the samples are at by far the greatest disadvantage. In most cases, individuals would find that their property was of very little economic significance to researchers. But more positively, it has been suggested that research might be furthered rather than hindered by the recognition of property rights, because those previously reluctant to come forward now have an incentive to do so (Lin, 1996). Furthermore, the mere recognition of property does not preclude altruistic gifting.

The second major counter-argument is, of course, that commercialization of body parts leads to the prospect of exploitation. This is undoubtedly true. But, merely because we face that prospect is no reason *in se* to refuse to recognize property rights as a matter of principle. Exploitation can be guarded against. Indeed, it is naïve to imagine that a black market in body parts does not already exist. It most certainly does.[14] To ignore the reality does not make it go away. Moreover, this argument is open to significant challenge as an example of undue paternalism. As Andrews (1995) argued in the context of surrogacy, it may be more devaluing to persons not to recognize their worth in monetary terms for the contributions they can make to society from the use of their bodies than it is to protect them from potential predators — provided, always, that the value they represent is not entirely reducible to those terms.

The exploitation argument also provides an example of an overly pessimistic view of the utility of self-ownership rights. Rather than prejudicing individual interests, the recognition of property rights can bolster the respect that individuals deserve and can at the same time provide a crucial means of ensuring that that respect endures. The wholesale application of a traditional property model to the human body and its parts is not, however, envisioned. This would be inappropriate and unacceptable in many respects. Yet, to the extent that a body property model reflects a desire and need to protect the human personality, certain key features of the language and operation of property rights could serve this end very well (Bray, 1990).

Researchers might object, however, that it would be impossible to monitor individuals' samples for these would invariably become mixed with others during the research process. But this is not problematic in property terms. The concepts of *commixtion* and *confusion* are well established in property law.[11] Where two separate entities are mixed together and cannot be separated, property in each element ceases and is replaced by common property in the resulting mixture. The new property is owned by each of the interested parties and must be held in trust for the benefit of all. So, if two piles of corn (solids are governed by *commixtion*) or two bottles of wine (liquids are examples of *confusion*) are merged the resulting property is owned in common by the owners of the original elements. So too with genetic samples. Indeed, the notion that property is to be held in trust is entirely apposite in this modern context. The benefits to be derived from the new property should accrue to all of those who have contributed. Alternatively, specification might occur when a new thing has been created without the knowledge or consent of the original owners, for example, where A builds a new house using B's bricks. B cannot claim the return of her bricks in such a case but she is nevertheless entitled to compensation for her loss. So too, once again, it might be with genetic samples. Matters may be more problematic, however, in the context of the ownership of information derived from samples. As has been stated, information is a difficult concept to fit into the property paradigm, but it is by no means impossible to do so (Valerio Barrad, 1993). Collective claims to property in information, such as familial genetic information, might therefore also arise.

Notes

1 Laurie (2002). I am grateful to the publishers for allowing elements of chapter 6 of this monograph to be reproduced here. A version of this paper was given at the IASTED Law and Technology International Conference in Boston, Massachusetts in November 2002.

2 See further, O'Neill (2002).

3 The European Group on Ethics in Science and New Technologies to the European Commission recognizes the same connection between personal health data and personality. See EGE (1999, para. 2.2).

4 Excised body parts that are not intended for another (such as transplant organs) or for return to the individual (such as stored sperm), are subject to the normal rules of personal property (Bundesgerichtshof, 1993).

5 ORS 659.700-720.

6 Senate Bill 114 was before the 71st Oregon Legislative Assembly (January 8 to July 7, 2001).

7 See also, Article 4 of the Universal Declaration on the Human Genome and Human Rights: "the human genome in its natural state shall not give rise to financial gains," while Article 21 of the Council of Europe Convention on Human Rights and Biomedicine states: "The human body and its parts shall not, as such, give rise to financial gain."

8 *Moore* v. *Regents of the University of California* 793 P.2d 479 (Cal. 1990), 271 Cal. Rep. 146.

9 See also HGC (2001: 20-22).

10 See, for example, Beyleveld and Brownsword (2000); Harris (1996); Morgan (2001, chapter 6).

11 See further, de Witte and ten Have (1997).

12 Examples include doing no harm and respecting individual privacy.

13 *HOWARD FLOREY/Relaxin* [1995] EPOR 541.

14 Ibid., at 550. It was left open, however, whether the research was immoral, but this was not addressed by the Division as it is a question outside its remit (the remit being to determine whether the granting of a patent would be immoral).

15 Directive 98/44/EC.

16 For a trenchant critique, see Beyleveld (2000).

17 For a defence of the role of autonomy and consent as a counter to property claims, see Skene (2002).

18 For a discussion, see Mason and McCall-Smith (2002), chapter 15.

19 See Mason and Laurie (2001).

20 *Moore* v. *Regents of the University of California* 793 P.2d 479 (Cal. 1990), 271 Cal. Rep. 146. See too, *Brotherton* v. *Cleveland* 923 F.2d 661 (6th Cir. 1991).

21 *Moore*, Cal. Rep. at 161.

22 Ibid., at 162-163.

23 Ibid., at 168. For comment on *Moore* see, Hoffmaster (1992).

24 See, for example, Beyleveld and Brownsword (2000); Boulier (1995); Valerio Barrad (1993).

25 On experiences to date of applying contract law to reproductive materials, see Vukadinovich (2000).

26 <http://www.pxe.org/>.

27 *Greenberg et al.* v. *Miami Children's Hospital Research Institute Inc. et al.*, (2003), pending. Jurisdictional issues were settled at Illinois (Eastern Division) District Court, (2002) WL 1483266 (N.D.Ill.).

28 Compare Ryan (1994) and Munzer (1994).

29 In *Hecht* v. *Superior Court* 20 Cal. Rptr. 2d 275 (1993), quoting *Davis* v. *Davis* 842 SW 2d 588 (1992), the California Court of Appeals held that stored sperm "occupies an interim category that entitles them to special respect because of their potential for human life," but that a deceased donor had an interest "in the nature of ownership, to the extent that he had a decision making authority as to the sperm...which falls within the broad definition of property in the Probate Code," at 281.

There is tentative Australian authority that stored human tissue can be the property of those from whom it was taken and their heirs, see *Roche* v. *Douglas* [2000] WASC 146. Note, however, that the Australian Law Reform Commission and the Australian Health Ethics Committee have recommended that the "common law right to possession of preserved samples, which is currently enjoyed by hospitals and others, should continue to be upheld, but full property rights in genetic samples should not be granted." See ALRC and AHEC (2002), chapter 17.

30 For an indication of the scale of the problem see Organ Watch at <http://sunsite.berkeley.edu/biotech/organswatch/>.

31 This terminology is drawn from Scots law, however, the concepts are well recognized in the laws of most western legal systems.

References

ALRC and AHEC (Australian Law Reform Commission and Australian Health Ethics Committee) (2002) *Protection of Human Genetic Information*, Discussion Paper 66.

Andrews, L.B. (1995) "Beyond Doctrinal Boundaries: A Legal Framework for Surrogate Motherhood," *Virginia Law Review*, 22: 2343.

Beyleveld, D. (2000) "Why Recital 26 of the E.C. Directive on the Legal Protection of Biotechnological Inventions Should Be Implemented in National Law," *Intellectual Property Quarterly*, 4: 1.

Beyleveld, D. and R. Brownsword (2000) "My Body, My Body Parts, My Property?" *Health Care Analysis*, 8: 87.

Boulier, W. (1995) "Sperm, Spleens and Other Valuables: The Need to Recognize Property Rights in Human Body Parts," *Hofstra Law Review*, 23: 693.

Bray, M.B. (1990) "Personalizing Personality: Toward a Property Right in Human Bodies," *Texas Law Review*, 69: 209.

Bundesgerichtshof (1993) BGHZ, November 9: 124, 52.

de Witte, J.J. and ten Have, H. (1997) "Ownership of Genetic Material and Information," *Social Science and Medicine*, 45: 51.

Greely, H.T. (1998) "The Control of Genetic Research: Involving the 'Groups Between'," *Houston Law Review*, 33: 1397.

EGE (European Group on Ethics in Science and New Technologies) (1999) "Opinion of the EGE, Ethical Issues of Healthcare in the Information Society," Opinion No. 13, July.

Halsbury's (nd) *Laws of England*, Fourth Edition, Vol. 20: Gifts, para. 1.

Harris, J.W. (1996) *Property and Justice*, Oxford: Clarendon Press.

HGC (Human Genetics Commission) (2002) *Inside Information: Balancing Interests in the Use of Personal Genetic Data*, May.

— (2001) *Public Attitudes to Human Genetic Information*, London, 2001.

Hoffmaster, B. (1992) "Between the Sacred and the Profane: Bodies, Property, and Patents in the *Moore* Case," *Intellectual Property Journal*, 7: 115.

HUGO (Human Genome Organisation), Ethics Committee (2000a) *Statement on Benefit-Sharing*, Vancouver, April 9.

— (2000b) "HUGO Urges Genetic Benefit-Sharing," *Community Genetics*, 3: 88.

Knoppers, B.M. (2000) "Population Genetics and Benefit Sharing," *Community Genetics*, 3: 212.

Laurie, G.T. (2002) *Genetic Privacy: A Challenge to Medico-Legal Norms*, Cambridge University Press.

Lin, M.M.J. (1996) "Conferring a Federal Property Right in Genetic Material: Stepping into the Future with the Genetic Privacy Act," *American Journal of Law and Medicine*, 22: 109.

Mason, J.K. and G.T. Laurie (2001) "Consent or Property? Dealing with the Body and its Parts in the Shadow of Bristol and Alder Hey," *Modern Law Review*, 64: 711.

Mason, J.K. and R.A. McCall-Smith (2002) *Law and Medical Ethics*, Sixth edition, Edinburgh: Butterworths.

Moore, A.D. (2000) "Owning Genetic Information and Gene Enhancement Techniques: Why Privacy and Property Rights May Undermine Social Control o the Human Genome," *Bioethics*, 14: 97.

Morgan, D. (2001) *Issues in Medical Law and Ethics*, London: Cavendish.

MRC (Medical Research Council) 1999 *Working Group on Human Tissue and Biological Samples for Use in Research: Report of the Medical Research Council Working Group to Develop Operational and Ethical Guidelines*, London.

MRC (Medical Research Council) (2000) *Public Perceptions of the Collection of Human Biological Samples*, London.

Munzer, S.R. (1994) "An Uneasy Case Against Property Rights in Body Parts," *Social Philosophy and Policy*, 11: 259.

O'Neill, O. (2002) *Autonomy and Trust in Bioethics*, Cambridge University Press.

Ryan, A. (1994) "Self-Ownership, Autonomy and Property Rights," *Social Philosophy and Policy*, 11: 241

Seeney, E.B. (1998) "*Moore* 10 Years Later — Still Trying to Fill the Gap: Creating a Personal Property Right in Genetic Material," *New England Law Review*, 32: 1131.

Skene, L. (2002) "Proprietary Rights in Human Bodies, Body Parts and Tissue: Regulatory Climates and Proposals for New Laws," *Legal Studies*, 22: 102.

Valerio Barrad, C.M. (1993) "Genetic Information and Property Theory," *Northwestern University Law Review*, 87: 1037.

Vukadinovich, D.M. (2000) "Assisted Reproductive Technology Law: Obtaining Informed Consent for the Commercial Cryopreservation of Embryos," *Journal of Legal Medicine*, 21: 67.

Part 3

Intellectual Property

Genomics Patents

John H. Barton

Many new forms of patents are being issued today in the genomics area. These patents create controversy, because they seem to be covering inventions rather than discoveries, because they have significant impacts on research and medicine, and because they seem to reach to the heart of life itself. Although this paper does not deal with the ethical issues implied by the last criticism, it does attempt to put these patents in legal context and to explore their economic implications. It concludes by discussing ways in which patent law might be revised to respond to the issues posed by these patents and placing those responses in the broader context of the global trends, which will affect the economics of applying genomic research to real-world medicine.[1]

Current Expansions of the Scope of Patentable Subject Matter

The fact that people are obtaining patents on genes and gene sequences is not new. Such patents have been issued since at least the 1980s, typically covering the sequences of natural genes and their associated proteins, where it is expected at the time of application that the protein might be a useful therapeutic. The monopoly conferred by the patent would cover isolated sequences, the purified protein, various vectors used to transform production organisms with the relevant sequence, and the transgenic organisms used to produce large quantities of the protein. In patent law theory, none of these existed in nature before, for they had not been isolated or purified (and the transgenic production organisms were, of course, novel). The scope of the monopoly rights is adequate to enable a pharmaceutical firm to invest in the clinical trials and other research needed to bring to market a product based on the therapeutic protein.

There have been several extensions of this pattern of patenting. One set of extensions involves patents on gene sequences where the therapeutic application is less direct. Thus, patents were granted on biological receptors that were unlikely to be therapeutics, but might be useful as drug targets, because a compound that interacts with an important receptor might be useful therapeutically. The patent in this situation would cover the use of the receptor in screening tests to identify new drugs — it would not bar use of live animal models in which the receptor was found as it had always been in nature, but would prevent others from creating the chemical and using it in an in vitro screen (clearly a much less expensive way of screening a large number of chemicals). Moreover, patents have been sought on partial sequences that might be used to identify a gene and on genes that are identified not by actually producing the protein but by computer analysis of a genome sequence. It was to deal with these patentability questions that the United States Patent and Trademark Office issued its Utility Examination Guidelines[3] in 2001, which lay down standards for how much has to be known about the biological significance of a sequence before the sequence can be patented.

What is less known is that patenting has extended much further. For example, the United States has now issued patents on protein co-ordinates (i.e., on the result of physical measurements of proteins to define their precise shape). The monopoly that is actually claimed in these patents is the use of the measured co-ordinates in computer programs to attempt to model the interaction of the protein with other chemicals that might be candidates for therapeutics. The patents thus supplement patents on receptors. The receptor patents attempt to control laboratory use of a receptor protein as a target to identify a therapeutic; these patents attempt to control computer simulations that might be used for the same purpose.

In addition, there are now patents on diagnostic sequences. These amount to patents on the information that a specific gene sequence in a person has particular implications for the disease susceptibilities of that person or for the likelihood that a particular drug will be especially beneficial or harmful for that person. In a sense, they are patents on the information that there is a particular relation between a genotype and a phenotype. The important, by now classical, example is that of the BRCA sequences that indicate susceptibility to breast cancer. The patent confers control over use of this information as a diagnostic test — and this is very broad control. It is not as if a patent covered the design of a particular way to measure blood pressure; it is rather as if the patent covered the use of blood pressure itself as a way to understand the physiology of a patient. The number of patents of this character is likely to increase, because more and more data are being collected through micro-arrays during large-scale clinical trials. These micro-arrays provide genomic sequence information that can be correlated with participant physiology to provide new information about genetic markers of disease and of drug susceptibility.

Economic Implications

For the pharmaceutical industry, many of these patents are a serious problem. Typically, the information about gene sequences or about protein structures that is covered by the patents described above is information of value in developing new pharmaceutical products. The patented gene or protein may itself be a possible therapeutic or it may be a target against which a therapeutic can be tested. Obviously, these bits of information or research tools are contributions to drug development, but economically, there is little or no independent value in these inventions or discoveries. The economic value derives from the final product (i.e., a pharmaceutical that is developed with the aid of the research tool).

Ultimately, there is one profit or monopoly rent from marketing the final product that must be divided between the pharmaceutical firm and those biotechnology firms that supply such research tools. These tools could be developed by the pharmaceutical firm itself. They have often, instead, been developed by biotechnology firms that concentrate on identifying such research tools and then supply them under contract to pharmaceutical firms, typically through a strategic alliance. By patenting these tools, the biotechnology firm improves its marketing position by using the threat (at least implicit) that any effort by the pharmaceutical company to use the relevant research information or method without permission will give rise to a claim for patent infringement. To avoid such threats, several members of the pharmaceutical industry, together with the Wellcome Trust, created the SNP Consortium, an effort to keep a large number of "single nucleotide polymorphisms" (gene positions that differ from person to person and may be useful in identifying particular genes) from being patented in ways that could be used against the industry's researchers.

From a policy perspective, the economic value of the patent on a research tool depends on the balance between the benefit of the patent in encouraging investment to create the research tool and the complication the patent creates for the firm using the technology. In turn, this depends on whether there are other incentives to develop the research tool (e.g., a public sector genomics program) or other ways the pharmaceutical firm can gain access to the information (e.g., by its own sequencing or measurement). Getting this balance right is one of the central issues in the genomics patent area.

For the diagnostic industry, the issues are somewhat different. A firm holding a genomics diagnostic patent has a very significant monopoly that, in effect, reaches the information covering the particular genotype–phenotype relationship. The patent also covers something very close to the practice of medicine — something that many nations regard as inappropriate for patent coverage, even when they accept patents on particular devices or products that may be used in the practice of medicine. Hence, these patents have given rise to significant opposition, exemplified by the major attack in Europe on the BRCA patent. The policy balance here, then, is quite different from that in the pharmaceutical area. Here the issue is whether the benefits the patents provide in encouraging research in developing new diagnostics outweigh the clear medical inconveniences of such patents.

These economic characteristics raise special issues for Canada, which, because of the character of its industry, faces a different policy balance from the United States. In general, a patent is territorial only, so patents granted in other nations, such as the United States, need not be respected in Canada unless the same invention is patented in Canada (or unless Canada intends to export a product to the United States). And, on certain of these patentability issues, there is reasonable space under TRIPS for Canada to adopt a different legal strategy from the United States. (TRIPS[1] is the most important international agreement governing patent law.) Thus, Canada might decide that, since it is more a consumer of diagnostic technologies than a developer of such technologies, it should not allow patents on those inventions that amount to discoveries of genotype–phenotype relationships. In contrast, the United States might be more interested in encouraging a diagnostic industry. Moreover, to the extent that Canada restricts patents on fundamental discoveries and gene diagnostic sequences, it becomes a more attractive centre within which to conduct biogenomic research, for such research can be conducted without patent infringement. At the same time, Canada must recognize that the patent laws affecting the strength of its genomics firms will be those of the United States and Europe, more than those of Canada, for it is these other areas that are more likely to contain the pharmaceutical firms with which Canadian firms will seek strategic alliances. For this reason, Canadian genomics firms will be more interested in obtaining patents in the United States and Europe than in obtaining patents in Canada.

Patent Law Responses

Devising an appropriate legal standard for patents in the genomics area is not easy. The patents reflect a fundamental tendency in character of research in the biotechnology and bioinformatics area. More and more fundamental discoveries are being made in these areas, these discoveries frequently have quite immediate commercial value, and nations want to use the patent incentive as a way to encourage the creation of industry in these high-prestige areas. Parallel pressures have led to the broad extension of patents to the computer software and informatics areas. Europe, for example, has a restriction on the patentability of computer programs "as such," and is finding it very difficult to hold this line in the face of constant innovation right at the line between patentable and unpatentable invention. These computer areas are closely related to bioinformatics and help explain the extension of patentability to genomics. Moreover, a patent law principle that is devised to be applicable to genomics has also to operate reasonably in the software context.

There may be other possible ways to draw a line that keeps patents in the genomics area from reaching too far, yet the strongest is probably to attempt to revive the distinction between invention and discovery. We all make such a distinction, even though we must sometimes grope for ways to apply it in cases that near the edge between invention and discovery. It does not seem reasonable to grant a patent on something that can be measured in nature. It must be admitted that US patent law does not formally make such a distinction and the US *Patent Act* states explicitly that "[t]he term 'invention' means invention or discovery."[1] Yet, even US courts regularly state that an abstract principle or a principle of nature is not patentable. Canada has a much more narrow definition of "invention" as meaning "any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter."[2]

Even if the distinction is revived, its application to the genomics area remains difficult and raises practical as well as theoretical principles. Few would deny that a natural protein or its sequence is appropriately patentable when the patent serves as the mechanism of supporting clinical trials to bring the drug to market. Yet, most of us would have trouble with patents that restrict the use by scientists of the information specifying the protein. Is the right answer to say that in the pharmaceutical case, the sequence is being used as the formula for the chemical (DNA or RNA) and should therefore be patentable, while in the research case it is being used primarily as information and should not be patentable? If such a distinction is adopted, it perhaps implies that diagnostic patents should not be granted, since in the diagnostic case the sequence is being used as a source of information. Yet this may not satisfy a policy goal of encouraging a diagnostic industry. We are facing genuinely difficult issues.

The Future

Two final points might be noted in this summary. First, this issue may move away from the national policy process. Negotiations going on at the World Intellectual Property Organization to harmonize international patent law may prove decisive. The long-term goal of these negotiations, at least for many, is to create a world patent. The short-term goal of the current negotiations is to harmonize patent law, so searches and judgments in one office can be relied on in others. This harmonization may well take away some of the freedom that nations now have to design their patent laws to include or exclude certain forms of genomic patents. The negotiations are being conducted by the patent community; they would benefit from outside input from the scientific and medical communities.

Second, as we think about the economic implications of these forms of patents for various forms of pharmaceutical and diagnostic industries, we should remember that these industries are facing economic pressures and may change radically. In spite of all the recent contributions of genomics and biotechnology to drug development, the number of new chemical entities

(NCEs) being developed by the pharmaceutical industry is falling in relation to the industry's research investment. With products coming off patent, the industry is in search of blockbusters, and is relatively less interested in high-risk low-payoff products. At the same time, we seem likely to see the key markets, even the US market, move more toward a public procurement model, especially for products such as vaccines. In such a situation, research and development may look more like that in the defence industry, where these costs are rather explicitly subsidized by the government (ideally in a way that maintains the opportunity for unconventional ideas to be pursued). In such a system, patents play a quite different role, if any, than they do in today's pharmaceutical industry. When we think of designing the patent system to serve the economic needs of industry, we must think of the industry the way we expect it will be over the 20-year lifetime of patents now being issued.

Notes

1 Since the Conference, an important study has been issued by the Nuffield Council on Bioethics, *The Ethics of Patenting DNA: A Discussion Paper* (July 2002). It explores many of the issues discussed here at greater length. The author was a member of the Round Table Meeting that developed the paper.

2 66 Fed. Reg. 1093 (Jan 5, 2001).

3 Agreement on Trade-Related Aspects of Intellectual Property Rights, Including Trade in Counterfeit Goods.

4 35 U.S.C. § 100.

5 *Patent Act*, Chapter P-4, Section 2.

Genetic Technologies, Health Care Policy and the Patent Bargain

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The idea of granting patents on human genetic material continues to cause controversy. The debate is largely focused on the moral acceptability of human gene patents, the impact of gene patents on the research environment, and the value of patents to stimulate innovation and the commercialization and dissemination of genetic discoveries. As highlighted by a recent controversy in Canada, patents can also have a profound effect on health policy and access to genetic services. Creative and bold patent reform initiatives are necessary to ensure that society will, to the highest degree possible, reap the health care benefits of the genetic revolution.

Since the inception of the Human Genome Project, the idea of granting patents on human genetic material has caused controversy. To date, much of the debate has focused on the moral acceptability of human gene patents (Resnick, 2001; Knoppers, 1999; Caulfield, 2000), the impact of gene patents on the research agenda and the research environment (Heller and Eisenberg, 1998; Bobrow, 2001), and the value of patents to stimulate innovation, and the commercialization and dissemination of genetic discoveries (Doll 11, 1998).

However, as highlighted by a recent controversy in Canada, patents can also have a profound effect on health policy and access to genetic services. In the summer of 2001, Myriad Genetics decided to take steps to enforce its patents over the BRCA1/2 genes. Provincial agencies throughout Canada received a letter stating that all genetic testing that utilizes the BRCA1/2 genes must now be done through Myriad's laboratories. Because of the cost associated with doing the tests out of country (more than C$3,800), a number of Canadian provinces have gone so far as to formally state that they will either ignore or fight the patent (Benzie, 2001). Across Europe, Myriad's actions to enforce a related patent have elicited a similar response (Watson, 2001).

But is Myriad really to blame? Isn't Myriad using its patent rights in a completely legal and logical fashion — to fully commercialize one of its products? In a world where gene patenting is viewed by a variety of stakeholders as an important part of the innovation process, and is encouraged by governments and universities alike, this scenario illustrates the importance of understanding and creating strategies to address the long-term health policy implications of the thousands of patents that have been issued or remain pending on human genes. In this brief article, we discuss the issues that flow from the conflict between gene patents and health policy. The paper is not meant to be a comprehensive analysis of all the ethical, legal, and social issues associated with gene patents or the patent system.

Impact

By granting a limited-term monopoly over an "invention," patents are meant to encourage innovation and the rapid dissemination of new technologies. Although the economic data are ambiguous (Gold, 2000; Sakakibara and Branstetter, 2001; Hall and Zeidonis, 1988), conventional wisdom maintains that this monopoly is required to ensure the growth and commercialization of useful technologies. Naturally, this monopoly gives the patent holder a great deal of power to control how the new technology will be used, the price to be charged and, to some degree, who will provide the service. In exchange for this monopoly, the invention is fully disclosed to the public. This is one of the trade-offs that is built into the patent system.

The downside of this loss of state control is most readily apparent in countries, such as Canada, that have a publicly funded health care system where global budgets may not be able to accommodate the demanded monopoly price. In such situations, the patent may result in a loss of public access to a necessary health care service. This can happen, because either the administrators of the public system decide they will not pay for the patented test or the patent holder simply refuses to allow access. Currently, unless there are formal price control schemes in place, patent holders are well within their rights to charge whatever they deem appropriate. In fact, one could argue that a justification for the patent system is to give patent holders the ability to charge a premium price, without the threat of competition, to reward the innovation process and allow a recouping of research expenses.

Interestingly, recent survey research done in Canada found that few of those surveyed had "moral or religious objections" to the patenting of human genes and a majority (63 percent) saw more benefits than risks associated with the patenting process (Pollara and Earnscliffe, 2000). However, in focus groups, it was found that there were major concerns based on issues of access and equity. In the context of health care, at least in Canada, access seems to be the dominant public consideration.

Limited-term monopolies are associated with several other health policy concerns, including a possible loss of quality control and the erosion of service delivery efficiency. For example, a laboratory that has developed a cheaper, more efficient way of delivering a given genetic service may be prohibited from doing so by the patent holder. Additionally, if overbroad patents are granted, the effect can be that further research in the field is blocked (Merges and Nelson, 1990; Roberts, 1994).

Harmonizing Health Care and Innovation Policy

The great irony of the Myriad controversy is that the patentee is doing precisely that which is encouraged by governments around the world. Both publicly and privately funded researchers are under increasing pressure to secure patent rights over their genetic "inventions." Indeed, in the university setting, the number of patents a researcher holds is often one of the factors considered in the CC academic promotion process. The hope, of course, is that some of these patents will lead to a commercialized product and thus facilitate the growth of the biotechnology sector for a given region.

From a health policy perspective, governments throughout the world are concerned with the containment of health care budgets. The introduction of new, and often expensive, health care procedures and technologies has been identified as an important factor in the rise of health care costs (Flood, 2000). Although genetic technologies may one day help reduce health care expenditures by facilitating effective preventive health care strategies, at present, genetic tests are largely viewed as another added expense (Benzie, 2001). As such, it is understandable that governments would seek to find the least expensive alternative.

So, can governments have it both ways? Can they have policies that are designed to promote the patenting process and, at the same time, actively fight the logical implications of those same patents? We suggest that a more realistic balance must be struck between innovation policy and long-term health care policy. We need to develop strategies that allow governments to both reap the benefits of the intellectual property system and maintain a degree of control over how the new technologies are used.

Possible Responses

There are several ways the issues associated with gene patents could be addressed. The most radical policy move would be to ban all human gene patents. In fact, this was recently recommended by the Canadian House of Commons Standing Committee on Health (Canada, 2001). However, the momentum of the biotech industry, the long history of patentability of gene sequences, and the impact and complexity of existing international trade agreements make this, at present, an impractical and unrealistic option. In addition, there are economic and ethical arguments for retaining patents in this context (Caulfield, 2000).

Another approach would be to address the problems associated with the gene patents on a case-by-case basis. That is, we could wait for court decisions to refine and clarify the existing patent criteria. But because patent jurisprudence will always lag behind the application of the science, such an approach is destined to fail as a means of producing timely patent reform. A case-by-case approach could never supply a comprehensive, and forward-looking, patent policy. Existing patent law has no means of incorporating health policy considerations into decisions about the appropriateness, scope, or possible infringement of a given patent, the three usual subjects of patent litigation. Thus, patent litigation can provide important refinements to the current system, but it seems unlikely to provide the broad-based policy reform needed.

A more promising policy option would be to develop a system that allows governments to override the patent holder's complete control over price and access. For instance, we could modify patent law so the price charged for a given genetic service is determined by an independent entity, and a "reasonable" fee would be guaranteed to flow to the patent holder. Such an approach provides policy makers with an explicit tool to balance the goal of stimulating innovation and controlling the impact of patents on health care policy. Patent holders would still retain a right to profit and a limited monopoly control over the "genetic invention," but the government could ensure that the needed genetic service was accessible within the health care system at a reasonable price. Although untested, it is arguable that such a licensing scheme would be permissible under existing international agreements. The *Agreement on Trade-Related Aspects of Intellectual Property Rights* (the TRIPS Agreement) allows compulsory licensing under certain circumstances. Although this agreement was not aimed at the issues associated with gene patents, it is an important recognition by TRIPS Agreement members that policy concerns may override economic and trade-related interests. Indeed, the recent Ministerial Declaration on the TRIPS Agreement and Public Health (WTO, 2002) states unequivocally:

> We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, ill particular, to promote access to medicines for all.

It could be argued that such an approach has the potential to introduce market uncertainty and, thus, remove a portion of the financial reward that allows patents to work as an incentive for innovation. This is a valid concern. However, as highlighted by the Myriad controversy, without some form of policy compromise, public access may be inappropriately compromised. In addition, it should not be forgotten that more radical options have been proposed, such as the outright ban on gene patents recommended by the Standing Committee on Health. In many respects, our more nuanced approach can be viewed as a fair compromise between two increasingly polarized positions.

Conclusion

We recognize that any reform to the patent system that could be viewed as weakening the economic value of patents will be met with a degree of resistance from both industry and those within government seeking to promote the innovation agenda. We also recognize that there are numerous valid and conflicting social values at play in this context that will make patent reform a tremendously challenging endeavour. Nevertheless, as more and more gene-related technologies move from the laboratory into clinical use, the relevance of gene patents to health care policy seems likely to increase substantially. Indeed, emerging technologies, such as multiplex testing and pharmacogenetics, have the potential to involve dozens, if not hundreds, of different gene patents at each clinical application (Evans and Relling, 1999; AMA, 1998). Creative and bold patent reform initiatives are necessary to ensure that society can reap the health care benefits of the genetic revolution.

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References

AMA (American Medical Association), Council on Ethical and Judicial Affairs (1998) "Multiplex Genetic Testing," Hastings Center Rep, 28: 15-21.

Benzie, R. (2001) "Ontario to Defy U.S. Patents on Cancer Genes: Province Will Pay for $800 Test, Not $3,850 Version by Myriad Genetic Laboratories Inc.: 'Share the Benefits'," *National Post*, September 20: Sect. A:15.

Bobrow, M. and S. Thomas (2001) "Patents in a Genetic Age," *Nature*, 409: 763.

Canada, House of Commons Standing Committee on Health (2001) "Assisted Reproduction: Building Families," (Chair: Bonnie Brown MP) December, Available at <http://www.parl.gc.ca/InfoComDoc/37/1/HEAL/Studies/Reports/healrp01-e.htm>. Accessed April 12, 2002.

Caulfield, T.A. and E.R. Gold (2000) "Genetic Testing, Ethical Concerns, and the Role of Patent Law," *Clinical Genetics*, 57: 370-375.

Caulfield, T., E.R. Gold, and M.K. Cho (2000) "Patenting Human Genetic Material: Refocusing the Debate," *Nature Reviews Genetics*, 1: 227-231.

"Doll 11: The Patenting of DNA," (1998) *Science*, 280: 689-690.

Evans, W. and M. Relling (1999) "Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics," *Science*, 286: 487.

Flood, C. (2000) *International Health Care Reform: A Legal Economic and Political Analysis*, New York: Routledge.

Gold, E.R. (2000) "Finding Common Cause in the Patent Debate," *Nature Biotechnology*, 18: 1217-1218.

Hall, B.H. and R.M. Ziedonis (1988) "The Patent Paradox Revisited: An Empirical Study of Patenting in the U.S. Semiconductor Industry 1979-1995," *Rand Journal of Economics*, 32: 101-128.

Heller, M.A. and R. Eisenberg (1998) "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *Science*, 280: 698-701.

Knoppers, B.M. (1999) "Status, Sale and Patenting of Human Genetic Material an International Survey," *Nature Genetics*, 22: 23-26.

Merges, R.P. and R.R. Nelson (1990) "On the Complex Economics of Patent Scope," *Columbia Law Review*, 90: 839-916.

Pollara Research and Earnscliffe Research and Communications (2000) *Public Opinion Research Into Biotechnology Issues: Third Wave*, Report presented to the Biotechnology Assistant Deputy Minister, Coordinating Committee, Government of Canada, December 2000. Available at <http://biotechnicalgc.ca/docs/engdoc/3Wavexec-e.pdf > Accessed December 21, 2001.

Resnick, D.B. (2001) "DNA Patents and Human Dignity," *The Journal of Law Medicine & Ethics*, 29: 152-165.

Roberts, T. (1994) "Broad Claims for Biotechnological Inventions," *European Intellectual Property Review*, 9: 371-373.

Sakakibara, M. and L. Branstetter (2001) "Do Stronger Patents Induce More Innovation? Evidence from the Japanese Patent Law Reforms," *Rand Journal of Economics*, 32: 77-100.

Watson, R. (2001) "MEPs Protest at Patent for Breast Cancer Gene," *British Medical Journal*, 323: 888.

WTO (World Trade Organization) (2001) "Declaration on the TRIPS Agreement and Public Health," Doc. WT/MIN(01)/Dec/2, Available at <http://www-svca.wto-ministerial.org/english/thewto_e/minist-e/min01_e/mindecl_trips_e.htm> Accessed April 12, 2002.

Whither Patented Genomics?

Kate Murashige

Introduction

"Genomics" is said to include genetics, proteomics, pharmacogenetics, stem cell research, and probably should also include molecular biology-based techniques and bioinformatics. Although many of these subject matters have implications for agricultural development as well as human medicine, the emphasis of this paper is on the latter. The players in "genomics" in medicine are descendants of the golden age of small molecule-based pharmaceuticals, where the availability of intellectual property has served the industry exceedingly well. Because most of the technology associated with genomics is not destined for ultimate consumer purchase, the value of intellectual property (IP) protection is measured in, perhaps, different ways. This paper will attempt to at least define the problems raised by the nature of this new technology and to delineate some proposed solutions.

Why Are Genomics Inventions Different?

The rationale behind protection for genomics-based inventions should be contrasted with that which has been used to justify "strong" patents on pharmaceuticals in the traditional sense. Although there is much complaining about the cost of patented prescription drugs, the response of the pharmaceutical industry is that the extraordinary cost of drug development, estimated in the range of $400 million to $900 million per successful drug, requires the security of an exclusive position once success has been achieved. Sales of a successful drug, such a Prilosec® or Prozac® are computed in the billions of dollars a year. Those billions would not be forthcoming were it not possible for the patent holder to exclude competition. According to the justification offered, by understanding that this control will be exercisable when success is achieved, the industry is willing to invest a substantial percentage of its profit in further research in the hope of finding the next winner. The cost of development of such a successful end product includes, of course, the cost of the many failures.

The mechanism for achieving this paradigm is almost a no-brainer. Desirably, the successful drug will be the subject of a patent claim, which has, hopefully, not expired by the time the drug has been approved. In the United States, limited extensions of term are available to compensate for time lost in the regulatory process, (35 U.S.C. § 156), and potential generic competitors are compensated by a statutory exemption for the research needed to secure regulatory approval prior to expiration of the patent (35 U.S.C. § 271(e)).

Of course, some inventions that were based on classical recombinant DNA techniques actually fit this picture quite well. Recombinant forms of tissue plasminogen activator, human insulin, human growth hormone, erythropoietin, interleukins, colony stimulating factors, and the like are really simply pharmaceuticals themselves, produced in a different way. Their development did raise some issues, much discussed early on, about the supposed contrast between discovery and invention (since these products, in terms of their basic nature, are products of nature), but this seems to have been subsumed by the more complex real world issues raised by modern genomics as defined above. In the United States, the patent system was stretched to fit by placing an emphasis on the information content of the natural product that defined its structure in the classic line of decisions starting with *Amgen, Inc. v. Chugai Pharmaceutical Co.*[1], and continuing through *Fiers v. Sugano,*[2] *In re Bell,*[3] and *In re Deuel.*[4] In these cases, the unpredictable nature of the structure that would ultimately be found carried the day to overcome any issue of obviousness. Perhaps the flip side of this focus is in the written description requirement as articulated in the *Regents of the University of California* v. *Eli Lilly,*[5] which has been used somewhat abusively by the US Patent Office.

Genomics as above defined, however, is a different kind of economic activity entirely. The patented subject matter is not destined for the ultimate consumer, it is destined for use within the research and development community itself. The methods, materials, and articles that are the subject of these patents are not, for the most part, subjects of extensive further testing and development; rather their use is achievable in their presently cast and claimed forms. They do share with traditional pharmaceutical-type patents the fact that the costs focused on their own perfection as tools may be considerable and, certainly, there may be a number of inevitable false starts whose costs must be factored in. But the claimed subject matter, such as a transgenic mouse, a technique for phage display, an assay system for agents that modify cells, or screening methods for compounds that will ultimately themselves be subject to patent protection as, for example, pain killers or AIDS treatments, are useable in their presently claimed form without the necessity for the massive development costs that are associated with optimization of formulation and dosage and regulatory approval.

The other property characterizing this claimed subject matter is that the end goal for its use does not lie in the use itself, but in its ability to assist in developing something else that will ultimately be useful (i.e., these are research tools). Since research is performed for the purpose of generating results, it can certainly be argued that the more people who have access to these tools, the more likely it is that these results will emerge. So the issue becomes one of providing sufficient incentive to develop the tools by assuring the developer that there will be no competition in providing these tools to users and assuring that enough people have access to them to make them useful to society as a whole.

No doubt the foregoing is somewhat oversimplified. There is a spectrum of research tool technology, which ranges from very focused tools, such as cloned opiate receptors, which might be used to screen for painkilling drugs, and tools which have wide application such as phage display techniques. However, even tools that appear to be focused, such as specific receptors, may turn out to yield results, which are not focused on single products or product types. It would appear that the thinking behind what should be offered in the way of intellectual property protection to research tools as a class may differ from the type of protection that is offered for consumer products (assuming, as generally it is, that researchers are not consumers in the traditional sense).

Criteria for Patentability and Genomics

It should be plain that the criteria for patentability are not designed to take account of the types of inventions that result from the general area of genomics. Ironically, the "solutions" to the inappropriateness of the standards of patentability to this technology are reflected in complementary ways in the United States and Europe.

The United States, as noted above, has foreclosed any possibility of attacking inventions derived from isolating or describing products of nature based on the lack of inventive step, since the criterion for patentability is non-obviousness; while the manipulations to obtain the resulting compositions or information may be well within ordinary skill, the results of applying those techniques are not predictable or obvious. Thus, to beat back the onslaught of applications providing information about structures as they exist in nature (and on processes that are based on an understanding of physiological mechanisms rather than on actual possession of means to control them), the United States has resorted to almost draconian requirements for written descriptions commensurate with claim scope and demonstrations of actual utility. The result has been thousands of applications replete with boilerplate disclosures attempting to forecast every possible property of compositions to be claimed and attempts to postulate structural characteristics to complement functionality. In Europe, on the other hand, the requirement for an inventive step would appear to require some mental activity on the part of the applicant, not just writing down unpredictable results. It has thus not been necessary to raise the bar on the utility counterpart standard (i.e., industrial applicability). Industrial applicability would certainly include research use as well as consumption by the general public.

There is no question, however, that the design of criteria for patentability did not contemplate the types of inventions seen today which involve isolation, identification, and manipulation of natural materials using predetermined techniques. (All inventions at some level involve manipulating natural materials, but supposedly in a way that involves creative imagination or at least serendipitous discovery.)

The question might be raised whether the concept of constructive reduction to practice has been taken too far in this context. Clearly, this is a useful concept in the context of standard pharmaceutical inventions. It would be ridiculous to require proof of clinical efficacy before patents could be granted on proposed drugs, and the courts in the United States have clearly appreciated this (*Burroughs Wellcome Co.* v. *Barr Laboratories, Inc.*,[6] *In re Brana*[7]). But is it not so clear that providing laundry lists of possible physiological effects or laundry lists of pharmaceuticals that are employable to obtain a particular physiological effect is serving a useful purpose? To take an example, the famous Human Genome Sciences patent 6,025,154 claims an isolated nucleotide molecule encoding the amino acids of what was designated as a chemokine receptor. Various speculative uses of the receptor were included in the patent specification, and the patent was granted on the basis of the work of others, which ultimately showed that the receptor was one used as an entry point for HIV. It is often asked: "What is the harm in just listing every physiological effect and specific disease in sight in order to provide a utility for a claim to a protein which can be characterized as a receptor on the basis of its general structure and then later selecting the right answer on the multiple choice test?" Would it not be simpler just to change the rules to require that there be some evidence that the receptor is connected with some phenomenon of interest and to, again by changing the rules, limit the scope of the claim to that area.

Alterations in Enforcement

If the criteria for patentability are problematic with respect to genomics subject matter, perhaps the problem can be attacked by altering the rules with respect to enforceability. Since the subject matter of most genomics patents is, in fact, research tools, one question often raised is whether the use of these tools falls within the research exemption, created by statute in other jurisdictions, but only by judicial fiat in the United States. The answer is that the research exemption in the United States is so narrow that it amounts to being non-existent in the context of the substantial research community that exists to exploit these tools. The narrow nature of this exemption was clearly enunciated in *Roche Products, Inc.* v. *Bolar Pharmaceutical Co., Inc.*[8] a decision which was reversed with regard to its specific facts with the passage of 35 U.S.C. § 271(e). The exemption to infringement created by § 271(e) is specifically, however, for activities related to obtaining Federal Drug Administration (FDA) approval for a drug. This carve-out may, however, have some implications for many of the research tools that are currently patented (*Abtox* v. *Exitronics*).[9]

The most recent case on this subject, *Embrex v. Service Engineering Corp.*,[10] only reinforces the narrowness of this exception. In that case, the research was conducted in an attempt to design around the patented subject matter, which involved injecting vaccine into eggs within the amnion or yolk sac.

It is obvious that there is no research exemption if there is any commercial purpose at all associated with the conduct of the research. This is particularly troubling in view of the increasingly strong nexus between university/institutional research and commercial sponsors. Every university worth its salt has an active technology transfer office, which seeks to provide a commercial outlet for research conducted at the university. Similar statements might be made about non-profit research institutes.

Possibly because of public pressure, it is considerably easier for workers in non-profit institutions to purchase and use research tools. Typically, a patented research tool may have a notice in the catalogue of its distributor that while a licence is granted for the use of the tool by purchasers from non-profit institutions, purchasers employed by commercial institutions must contact the patentee or the patentee's agent to obtain terms for a commercial licence. This possibility arises, of course, because many of the research tools are replicable and need only be purchased once. Thus, for example, research tools, which comprise DNA, can readily be replicated by the purchaser. While it is probably an abuse for the patentee to double-dip by charging a royalty on the initial sale of the tool, and again on its use, this may not be the case where the use extends far beyond the actual material that was originally purchased.

There does not seem to be a great deal of objection to the practice of expecting commercial entities to pay for the use of research tools as long as the licensing fees are reasonable. For example, the several patents managed by Dyax Corporation, which cover various aspects of phage display, are offered under terms of a commercial licence, which has been agreed to by over 50 companies. The licence terms include reach-through royalties but, apparently, the general terms are sufficiently economically acceptable that licensees can be found. The phage display technique has wide application, and it is recognized that retaining rights to practise a technology in a single entity would considerably slow the progress of biological research in general. Thus, this solution appears at least at some level to be acceptable.

A similar case in point which has received fairly recent publicity is that of the use of Harvard's oncomouse, a patented transgenic animal licensed to DuPont, from whom permission to use the mouse must be obtained. There are three issued US patents covering the oncomouse, the earliest of which issued in 1988 (US patent 4,736,866) which covers a transgenic non-human mammal, all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal or an ancestor at an embryonic stage. That patent expires in 2005. US patent 5,925,803 issued in 1999 covers screening using this type of animal, although these claims are limited to mice. That patent won't expire until 2016. US 5,087,571 issued in 1992 contains claims to cultured cells from transgenic mammals.

In the May 17, 2002 issue of *Science*, at page 1212, a report appeared entitled "DuPont Ups Ante On Use Of Harvard's Oncomouse." The article reports that DuPont is becoming more "assertive" about enforcing the conditions of an agreement reached with the National Institutes of Health (NIH) in mid-1999, which permitted non-commercial use of mice covered by the Harvard patents as long as non-profit institutions were conducting this research. The use is without payment of a fee. However, according to the terms of this agreement, if the mice are to be transferred to for-profit institutions or are to be used, for example, to screen compounds or test compounds that are destined for a possible commercial purpose, suitable material transfer agreements must be in place and fees must be paid. The academic institution must provide notice to DuPont of any such transfers or arrangements. There is also a requirement that NIH provide to DuPont any materials that are covered by these patents that it, itself, makes, without cost if DuPont so requests.

Another concern is that the claims issued in these patents are sufficiently broad to cover mice other than those described specifically in Harvard's patent applications which mainly discuss insertion of oncogenes, while cancer-susceptible mice can be made in similar ways by knocking out cancer suppressors such as p53.

Thus, although licences have been offered to permit use of research tools, there appears to be some concern with regard to the effect even of these licences on the progress of research.

Compensated Fair Use: A Proposed Solution

Under at least US law, there is no obligation on the part of a patent holder to permit others to practise the patented technology during the patent term (i.e., to grant any licence to others). Indeed, there is no requirement for the patent holder to practise this technology either. While it is difficult to find instances where a valuable research tool has been simply allowed to lie fallow, this is at least a theoretical possibility. It may very well be that only pressure exerted by institutions, such as universities and the National Institutes of Health, has resulted in at least the theoretical availability of licences on almost every research tool that is not being directly exploited for commercial purposes by its developer.

Indeed, there are occasional patents on research tools that have been filed for the specific purpose of offering licences and exacting licence fees. Perhaps the best known example is the multiplicity of patents issued to a Dr. Housey; efforts have been made to force a long list of companies to obtain licences to this technology. The recent District Court decision in *Bayer AG* v. *Housey Pharmaceuticals*[11] is part of this pattern. Claims in Housey's patent 4,980,281 are directed to a method to determine if a compound is an activator or inhibitor of a protein by treating two cell lines with a test compound, where one cell line contains a reporter protein and the other does not, and comparing the results. Bayer requested declaratory judgment for invalidity, non-infringement and patent misuse; Housey's motion to dismiss the complaint for patent misuse was denied since the proposed licence would extend the obligation to pay royalties on compounds identified by Housey's method beyond the expiration of the patent.

However, there is a theoretical possibility that a patentee might preclude the use of a research tool altogether.

One proposed approach is described by Janice M. Mueller, Associate Professor at the John Marshall Law School, in a January 2001 article in *The Washington Law Review*. This proposed solution envisions the ability of researchers to use any research tool, but with the obligation to pay a royalty on any product developed using the tool. The proposed reach-through royalty would be based on the profits made by the user. This would be one form of what is pejoratively called compulsory licensing, but which might also be designated by the less inflammatory term "compensated fair use."

In principle, this seems a plausible approach. But, of course, the devil is in the details. Two problems that immediately come to mind are the problem of stacking royalties where, as is often the case, a multiplicity of research tools may be required to identify and develop a commercial product and the dilemma of the patentee whose business it is to develop research tools, which then are offered for sale as the source of the patentee's own profit. Where these tools are themselves replicable, and thus need be sold only once to practitioners, the compensation for development of these tools may be too little, too late. Indeed, there may never be a commercial product identified using a particular research tool.

Conclusion

Intellectual property presents a unique challenge in its application to genomics, because inventions related to gene sequences, especially, are too easy to come by, can be claimed in ways that overlap, and are produced in the context of a society where the profit motive is strong and public spirit to move science ahead is weak. Coping with the problems created by this situation may reside in rethinking the nature of subject matter for which patent protection is granted, tailoring the standards of patentability to fit the reality of development in this area, and creating nuanced definitions of infringement or creating exemptions. Any such solutions, of course, should ensure fair compensation to patentees whose inventions are actually used by others but define this fairness in such a way that the possibility of windfall profits will not stand in the way of scientific research.

Notes

1 18 USPQ2d 1016 (Fed. Cir. 1991) cert. denied, 502 U.S. 856 (1991).

2 984 F2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993).

3 999 F2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993).

4 34 USPQ2d 1210 (Fed. Cir. 1995).

5 119 F3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

6 40 F3d 1223, 32 USPQ2d 1915 (Fed. Cir. 1994), cert. denied, 115 S. Ct. 2553 (1995).

7 34 USPQ2d 1437 (Fed. Cir. 1995).

8 733 F2d 858; 221 USPQ 937 (Fed. Cir. 1984).

9 122 F3d 1019, 43 USPQ2d 1545 (Fed. Cir. 1997).

10 216 F3d 1343 (Fed. Cir. 2000).

11 61 USPQ2d 1051 (DC Del. 2001).

From Darwin to the Genome: Secrecy and the Integrity of the Scientific Enterprise

Liam Brunham
Michael R. Hayden

Privacy of research data and materials can occasionally come into conflict with scientific obligations to share those data and materials. This has serious implications for the integrity of science.

At a recent international genetics meeting, an abstract entitled "Genes for obesity and anxiety" promised "linkages to several chromosomes." At the talk, however, no data were provided regarding either the identity or chromosomal location of these genes, apparently because of proprietary restrictions of the collaborating company.

This behaviour, though earning the researcher recognition at an international conference, failed to meet an obligation to provide sufficient data to assess or even interpret the claims being made. The result is an uninterpretable talk and demoralization to the scientists who attended to learn what the abstract had promised.

A more well known example of this practice is the Celera version of the human genome sequence, published in *Science* in February 2001 (Venter et al., 2001). Despite *Science*'s data deposition policy, which requires "deposition of the data before publication in an approved public database such as GenBank, SwissPROT, or PDB," the Celera sequence was deposited in the Celera proprietary database. Free public access to the data is restricted, for example by a maximum weekly download limit.

What is the result of such a breach of accepted practice? The scientific community is, as a consequence, unable to assess the research. For instance it becomes difficult to validate Celera claims that the sequence contains

25,588 genes, or that it is 1.1 percent exonic. The cumulative nature of the scientific enterprise is such that essential activities, such as replication and self-correction, cannot occur without free access to the data. Restricting access to published data compromises the ability of science to advance.

Of course one need not publish. A researcher may certainly choose not to publish, and accept the risk that someone else will take credit for the work first. It is instructive to consider the historical example of Charles Darwin, and consider what prompted him to publish his insights into natural evolution. Darwin kept secret his findings for 20 years, recognizing that his lack of understanding of the mechanism of inherited variation was a fatal flaw in his theory. Finally in 1859, he did publish *The Origin of Species*, prompted largely by his realization that Alfred Wallace was coming to similar conclusions about the nature of evolution (Zimmer, 2001). At that point, Darwin's desire to rightfully take credit for his work superseded his desire to hold off publication until he could develop an irrefutable theory.

These opposing interests become especially apparent in the case of industrial researchers. For the scientist in industry, there is a struggle between garnering intellectual credit through publication and maintaining secrecy to provide the time for priority in developing products and making further discoveries. The catch is that you cannot have it both ways; credit comes at the expense of secrecy. Celera wanted both: credit for its work through publication, but also secrecy through restrictions on access to the data. These restrictions, of course, served to protect the interests of the investors by allowing them to offer an unrestricted product at a fee.

It is tempting to consider data withholding as a problem of industry, but the evidence suggests that it is endemic to both the academic and industrial worlds. A recent survey of 1,240 geneticists from the 100 US universities receiving the most National Institutes of Health (NIH) funding provides some dramatic conclusions Campbell et al., (2002). Forty-seven percent of the geneticists surveyed reported having a request for information, data, or materials denied during the past three years. Twelve percent had denied another academic's request for information, data, or materials during the past three years. And strikingly, 28 percent had been unable to replicate a published result, because of another scientist's unwillingness to share data.

The authors of the study conclude that "data withholding occurs in academic genetics and it affects essential scientific activities such as the ability to confirm published results."

These three episodes represent serious threats to the integrity of the scientific enterprise. Science's integrity relies on the principles of full disclosure, and these principles require community standards to be enforced. The consequences of failing to meet these standards are a slowing down of research, unnecessary duplication of work, and a loss of public confidence.

None of this is new. Michael Polyani (1962) remarked 40 years ago that "in the absence of further information about the results achieved by others, new problems of any value would cease to arise, and scientific progress would come to a standstill."

There are many ways in which the "results achieved by others" can be disclosed. One ominous trend is the appearance of press releases, such as this one from DeCode Genetics: "DeCode and Roche announce the location of genes linked to obesity and anxiety" (September 11, 2001). It should be noted that this use of the term "linked" is fundamentally misleading as the distinction between genetic linkage and gene isolation is not at all made clear to the reader. These announcements are not associated with any simultaneous publication or peer-review process. They are essentially advertisements to investors dressed in scientific guise.

Press releases that promote unvalidated scientific results undermine public confidence in the scientific enterprise by making promises and raising hopes that are often not followed up on. This makes it difficult for the public to differentiate legitimate scientific milestones from these pronouncements. Ultimately, everyone loses: science is trivialized, the public loses confidence and, eventually, investors lose confidence as well, yielding an effect precisely opposite to what was intended. Press releases, if science-based, should be associated with validated, peer-reviewed scientific data.

Two forms of disclosure better suited to scientific advancement are patents and publications. Patents have existed since at least 1685, when Henry Oldenberg, Secretary of the Royal Society, created the *Philosophical Transactions of the Royal Society of London*, which served a function similar to patents today (Guedon, 2001). A patent is a social contract, whereby in exchange for full disclosure, one receives a limited monopoly on one's invention. Others must be able to replicate the achievement.

Publishing is also a social contract. It earns a researcher intellectual credit. In exchange, there is an obligation to provide data and materials sufficient for others to replicate the work. These issues continue to cause problems today.

Recently, a European scientist refused the request for published materials from an Israeli researcher, citing Israeli military aggression in Palestine as the grounds for refusal. In a June 7, 2002 editorial, *Science* editor Donald Kennedy wrote, "personal political convictions do not trump authors' obligations to share experimental materials."

Regarding both patents and publications, the ideal is a level playing field between both industry and academia. That is, regardless of who submits either a publication or a patent, the obligation is the same: full disclosure.

Full disclosure is essential to maintain both scientific integrity and public support of research. However, these principles are frequently breached. What should be done to address these problems? Solutions are emerging, and some are already in practice.

One solution is that journal editors should act as gatekeepers in enforcing the sharing of published data and materials. To a certain extent, this is already occurring. For instance, the *Nature* instructions to authors state that "as a condition of publication, authors are required to make materials and methods freely available to academic researchers for their own use" (*Science*, 2002).

Science was recently challenged over its data deposition policy as it was applied to the Celera human genome sequence. Editor Donald Kennedy (2002b) responded, "would we ever make another exception? Not likely, but...'never' is a long word."

Finally, the public and private sectors must together embrace conduct that enhances public confidence in science and research. This includes adherence to standards regarding data sharing, and equality between the standards applied to industry and universities.

These issues are being addressed. The National Academy of Sciences recently convened the Workshop on Community Standards for Sharing Publication-Related Data and Materials. A consensus emerging from this discussion is that it is the responsibility of authors to take reasonable steps to make promptly and readily available data that enables future replication and advancement of science (Board of Life Sciences, 2002).

Scientific integrity is challenged by data withholding, and public confidence is jeopardized by unvalidated claims. The antidote to these challenges is the establishment of community standards to ensure acceptable practices.

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References

Board of Life Sciences (2002) Workshop on Community Standards for Sharing Publication-Related Data and Materials, Washington DC. February 25, 2002.

Campbell, E.G. et al. (2002) "Data Withholding in Academic Genetics: Evidence from a National Survey," *Journal of the American Medical Association*, 287: 473-480.

Guedon, Jean-Claude (2001) *In Oldenberg's Long Shadow: Librarians, Research Scientists, Publishers, and the Control of Scientific Publishing*, Annapolis: ARL Publications Distribution Center.

Kennedy, Donald (2002a) "When Science and Politics Don't Mix," *Science*, 296: 1765.

— (2002b) in response to Philip E. Bourne, "*Science's* Policy on Data Deposition," *Science*, 296: 1609.

Polanyi, Michael (1962) "The Republic of Science: Its Political and Economic Theory," Minerva, 1, pp. 54-73; repr. in his *Knowing and Being*, Chicago: Chicago University Press, 1969, pp. 49-72.

Science (2002) <http://www.nature.com/nature/submit/gta/index.html#5.4> Accessed June 14, 2002.

Venter, J.C. et al. (2001) "The Sequence of the Human Genome," *Science*, 26: 1304-1351.

Zimmer, Carl (2001) *Evolution: The Triumph of an Idea*, New York: HarperCollins.

Part 4

Implications for the Developing World

Biotechnology's Foreign Policy[1]

Carl B. Feldbaum

We need a foreign policy for our great transformational endeavour that is biotechnology. We need such a policy now to decently and properly position our industry for the future.

From its inception, biotechnology has been a uniquely international enterprise. An American and an Englishman working together elucidated the structure of DNA almost 50 years ago; more recently, the Human Genome Project linked researchers around the world, from the Baylor College of Medicine in Houston to the Beijing Human Genome Center.

Today our industry's researchers hail from African villages and Manhattan high rises; from Munich and Melbourne; from London, Ontario, and London, England; from Scotland and Nova Scotia — New Scotland; from Calcutta and Calgary. But in the beginning, the infrastructure that supported these efforts — intellectual property, venture capital, streamlined technology transfer — was less widely dispersed and the world's brightest biotech researchers clustered in only half a dozen scientific meccas.

Previous technological revolutions have spread around the world. Think of the domestication of animals and agriculture, the development of the printing press, the assembly line, television, and the Internet. Following in their footsteps, biotechnology's global diaspora seems inevitable, especially since governments are promoting it. Japan has launched an ambitious program to build a national biotech industry 1,000-companies strong by the year 2010. Taiwan and Singapore have each pledged to invest hundreds of millions in US dollars directly into biotech companies. Such programs have already worked wonders in Germany and Israel. Both nations combined generous incentives with streamlined technology transfer from world-class research institutions to build dense biotech corridors.

So it seems appropriate to host our annual meeting outside the United States, here in Canada, home to the world's second-largest concentration of biotechnology companies, more than 360 firms strong.

But as our science and business emigrate from early strongholds in the United States, Canada and Europe across oceans and borders and into new cultures, international tensions over biotechnology continue to grow. In just the last few years, controversies have roiled over research and development spending priorities, genetic patents, bioprospecting, transgenic agriculture, and drug pricing.

These controversies stem from three separate forces. First is our shared desire to distribute the benefits of biotechnology as widely and as equitably as possible: both the products and the economic benefits the industry brings. Second, there is the hard but realistic need to earn back a return on one's research and development investment. Finally, there is the determination in some circles to hold our technology at bay, to halt the spread of biotech crops and certain other technologies, such as stem cells, that may change trade balances, threaten entrenched agricultural interests, or question tradition or religious values.

My premise today is that our industry needs to formulate its first foreign policy, one that is cognizant of the miserable judgments and mistakes of other industries — and avoids them. Our goal must be to ensure the widest possible dissemination of biotechnology's benefits while respecting the diversity of the world's nations and peoples. For a model, I looked to President Woodrow Wilson's Fourteen Points, which articulated his international goals after the carnage of World War I. Wilson's vision, once considered naïve, was to distribute the benefits of democracy while respecting the differences among nations.

Since we live in an age of e-mail brevity, I will limit the foreign policy points to my top 10. Here they are.

1. **The industry must work with governments and international bodies to integrate biotechnology into compelling responses to public-health crises.** The resurgence of threats to public health — from the AIDS pandemic in sub-Saharan Africa to the anthrax attacks in the United States — sharply reminds us of our vulnerability to humankind's age-old microbial nemeses. People in developing nations need no reminder. Almost 11 million children die each year of diseases that are preventable or treatable.

Addressing this perennial public health catastrophe demands actions that improve nutrition, sanitation, and water supply. In many regions, war and population displacement have magnified the effects of extreme poverty, leaving millions without access to even the cheapest antibiotics and vaccines. Forgive me, but genomics alone cannot solve these problems.

But biotech research and development can do its part in the developing world by producing vaccines that don't require refrigeration and are nasally or orally delivered. That investment in prevention can be made alongside continuing investment in diseases that afflict wealthy societies, especially as incomes rise and life spans lengthen. Although some have attacked this disparity in research and development investment, I counter that health care need not be a zero-sum political battle between disease constituencies or between industrialized and developing nations. Particularly in the private sector, substantial financing is always available for yet another fine idea, provided the proper market and regulatory mechanisms are in place. Which brings me to my second point...

2. **Biotech health leaders must devise an orphan-drug program for diseases of the developing world.** For a model of how we might stimulate expansion of research into diseases that plague developing nations, such as malaria, cholera, tuberculosis, and sleeping sickness, we might look to the successful US orphan-drug program, which governments in Europe, Japan, and elsewhere have emulated or are considering. The *US Orphan-Drug Act* of 1982 created incentives, such as clinical trial support and market exclusivity for companies that develop products to treat orphan diseases (i.e., diseases afflicting fewer than 200,000 Americans). The program has been an enormous, unequivocal success. In the decade before its launch, fewer than 10 drugs and biologics were commercialized for rare diseases; in the years since, more than 200 drugs and biologics for rare diseases have reached the market. These drugs treat everything from lead poisoning and growth disorders in children, to leprosy, leukemia, hemophilia, and juvenile rheumatoid arthritis. To support my point, all this was achieved while research and development investment in biotech increased for diseases affecting much larger populations. I pledge that BIO will work with the US Administration and Congress to create powerful incentives for companies to tackle diseases of the developing world. And we will work with our Canadian and other international partners to do the same.

   Once such drugs are developed, working out their means of distribution will undoubtedly be a contentious process, given the multitude of parties involved and their disparate economic and political interests. The

US biotech sector will need much closer, more trusting and trustworthy relationships with foreign governments, the World Health Organization, and non-governmental organizations (NGOs) like Médicins sans Frontières — Doctors Without Borders.

3. **Agricultural biotechnology must be more seriously considered as a significant part of any program to address the nutritional needs of the developing world.** Unfortunately, and somewhat ridiculously, this issue is relegated in some developed nations to triviality in the tabloids. The tabloids are trivial? What a surprise. But what is surprising — amazing really — is that the tabloids actually lead this public debate in some developed nations. For many of our African and Asian friends — an increasing number here in this room — this matter needs to be taken much more seriously, and now. Put simply, biotechnology provides new tools to plant breeders to accelerate the development of new varieties and hybrids. As we have already seen, new plants can combat vitamin and mineral deficiencies by making crops, such as cassava and rice, more nutritious, and they can increase yields by boosting disease resistance and improving plant hardiness in hostile environments. Not trivial benefits to people in developing nations.

   Once again, we need to find new, trustworthy ways of working with foreign governments and NGOs on the many "orphan-crops" that are not internationally traded commodities but are critical staples for the world's poorest people living in some of the world's harshest environments. Already, biotechnology companies have taken the lead by donating the genome of rice — a landmark event because, of all the grains, rice is closest to the ancestral grass from which all the world's important seed grains have evolved. Knowledge of its genome will be fundamental to improving many crops. Our researchers are working hard on such projects as disease-resistant, more productive sweet potatoes, a staple crop in sub-Saharan Africa.

   All this is not some version of technocratic colonialism. Researchers and political leaders of developing nations are in fact the most ardent supporters of biotechnology-based solutions to hunger and ill health. Listen to UN Secretary-General Kofi Annan, a citizen of Ghana. He has charged world leaders with facing "the implications of a steadily shrinking surface of [farmable] land, at a time when every year brings many millions of new mouths to feed. Biotechnology," he says, "may offer the best hope, but only if we can resolve controversies and allay the fears surrounding it."

4. **Markets should be open for demonstrably safe and effective biotechnology products.** I touched on part of this a minute ago. Particularly in Europe, "Franken foods" hype has been used to erect ill-founded trade barriers to biotechnology-enhanced crops, including a lengthy moratorium on new crop approvals. But now, we're also fighting those who would like to use the Biosafety Protocol and Codex Alimentarius as trade barriers to biotech food and agriculture products. We would hope that global regulatory systems, particularly those already guided by international treaties, are not hijacked in spasms of anti-Americanism. There, I've said it. Which brings me to point five...

5. **For biotech's positive outcomes to truly flourish, we need to agree that both international and national regulatory regimes be based on science.** As more and more nations upgrade their regulatory systems to consider complex biotechnology products, we urge them to detach that process from politics and ideology, even superstition. This is not easy. In the United States, Canada, everywhere, every new technology inevitably provokes a political confrontation between alarmists and the scientific community. And it always has. Back in the 1970s, when the US industry began, recombinant DNA itself provoked a wildly irrational response. The Mayor of Cambridge, Massachusetts no less, once proclaimed: "God knows what's going to crawl out of the laboratory!" He appointed a commission to study the clear and present danger that Harvard's Petri dishes posed to the local townspeople. What, in fact, crawled out of Cambridge labs were a generation of new therapies for deadly diseases including Gaucher's disease, and beta-interferon for multiple sclerosis.

   Back then, the protocols for managing biotechnology were developed by researchers and regulatory officials who scrutinized the data and saw that the risks were negligible and could be contained. The research moved forward and, today, recombinant DNA experiments are performed in high school science labs. And not just in Cambridge, San Francisco, or Seattle. I am talking about high school labs in Trumbull, Connecticut, and Hailey, Idaho. Again and again, the science proves the alarmists wrong.

6. **Regulations or at least applications should be harmonized, as much as possible, across international boundaries.** Such efficiencies will save a great deal of duplication of effort, which could get some life-saving therapies to many patients in the nick of time. I'm happy to report these efforts are already under way. With very little fanfare, last year the International Conference on Harmonization approved the Common

Technical Document (CTD), a drug-approval application format for use in Japan, Europe, and the United States. In some cases, it will save additional testing and months of reformatting. In addition to the CTD, the organization has quietly issued dozens of guidelines to standardize drug development requirements and is working on international standards and information-sharing guidelines for areas of drug regulation, such as quality control and safety pharmacology. BIO salutes them. Although it can take years of negotiation to reach regulatory compatibility, we hope such international co-operation among regulators becomes the norm.

One final area of harmonization that is critical to the growth of our global industry is the creation and acceptance of a common bioinformatics language to be used by researchers worldwide. I am speaking of the integration and interoperability of informatics tools known as I3C. It's good to have your own acronyms. But seriously, if our international community is to reap the health benefits inherent in genomics and proteomics we need to ensure that the best informatics tools are available and usable by everyone. To this end, BIO has joined with IBM, Sun Microsystems, The Whitehead Institute, Millennium Pharmaceuticals, the University of Manchester and over 100 companies and institutions worldwide to establish that common language.

7. **Efforts to expand the reach of biotechnology and streamline its regulation will be for naught if governments refuse to respect biotechnology-based intellectual property.** You know the importance of this issue. BIO has fought this battle for a decade now. For the 90 percent of biotech companies that have yet to bring a product to market, patent portfolios are their only assets. What a biotech company owns and markets are essentially ideas, for example, the discovery of a potential point of intervention in a disease process or the identification of a gene or inhibiting compound that might affect that process. But the work only begins there, even though the company may well earn a patent. Without patents to provide some period of market exclusivity, the hard, cold fact is that researchers and investors would never dream to recoup their investment in research and development. Without stable national and international systems of intellectual property protection, biotech enterprises and the benefits they bring are simply not possible.

8. **The implications of what has come to be called "bioprospecting."** Within the world's millions of species lurk genes, proteins, and hormones that can be used to treat diseases of humans, other animals, and many plants. **As researchers prospect for them, we must follow ethical guidelines that respect cultures and ensure fair compensation to**

indigenous peoples. BIO is developing a set of principles for our members, most of whom are inexperienced in negotiating, say a royalty deal with a provincial government in Peru. The principles would include provisions for informed consent and benefit sharing. The process will engender a host of complexities, for example, how are rewards to be distributed if a useful medicinal plant is native to more than one region? How do we recognize intellectual property arising from "folk" medicine? Some of these matters require international co-operation and treaties, but we believe first and foremost that our member companies must respect the laws of nations and cultures of localities where they perform research.

9. **The biotechnology industry must promote biodiversity on the path to achieving sustainable development.** Not only is biodiversity worth preserving in its own right — as the product of billions of years of evolution that can never be replicated — it is of course a critical raw material for our industry. We can contribute to biodiversity preservation. We can identify and analyze new or formerly unknown species in our quest for promising compounds and genes, the precursors of products.

   As you know, the core concept of sustainable development is to proceed with economic activity as a means of eliminating poverty, while at the same time placing equal weight on environmental protection. Today, sustainable development may actually be closer to our grasp because of industrial biotechnology. It is a versatile tool for producing renewable energy, reducing water and natural resource consumption, lowering production of greenhouse gases, and minimizing the generation of toxic waste — not simply removing toxic pollutants but preventing pollution at its source.

   Perhaps there has never been a more important time for us to move away from petroleum-based economies toward renewable carbohydrates. Companies are already using advanced proteomics in making ethanol fuel and plastic from corn sugars and soybeans. Consider what that means, especially today.

10. Looking back to September 11th brings us to my 10th and final point, that **biotechnology should be used to develop treatments and protective products for both military personnel and civilians, but it must never be used to develop weapons.** This point really needs no explanation.

September 11th also raised practical issues about security at companies and university labs engaged in biotech research. In the United States, legislation was proposed that would have severely restricted access of foreign nationals to biological materials, and the Commerce Department reminded companies and labs of previously unenforced government regulations concerning sharing sensitive technical information with foreign nationals. For our industry, which depends on the rapid cross-fertilization among the best ideas and the brightest people, such measures are anathema. Somehow we must guard security while maintaining the largely unfettered flow of ideas and people in the industry — a flow that's especially vital to those nations just beginning to build a biotech industry.

US Secretary of State, Colin Powell, has said that now is the time to combine "science and statecraft." He's talking to us. BIO wants to work with national and local biotechnology organizations around the world. I realize that as a US-based association we risk seeming arrogant in raising and addressing these issues. But I hope that the 10 points I have listed today will serve as points of departure for what should be a constructive conversation. As Winston Churchill said: "Courage is what it takes to stand up and speak; courage is also what it takes to sit down and listen."

Biotechnology products, issues, dilemmas, and consequent controversies are reaching around the world. Our researchers spring from every corner of the planet, and our science can now benefit the health, agriculture, industry, and environment on every continent and indeed, even in the oceans between. Any endeavour with such reach and responsibility can be well served by a few modest overarching principles.

So today I've proposed 10 points of a biotechnology foreign policy. But there's really little foreign about them. Among the folks in this room, at this international conference, representing over 50 nations, who is the foreigner? We are all in this great endeavour together, and I believe we are wise enough to learn from the mistakes of other industries and get our international responsibilities set right this time. Working together, we will take this endeavour to the next step and beyond.

Note

1 Adapted from a presentation given at BIO 2002, June 10, 2002, Toronto.

Bridging the Health Genomics Divide: A Case for Building Research Capacity in the South

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Despite substantial gains in global health over the past several decades, inequities between populations in the South and their counterparts in the North have increased. Furthermore, because health status is so dependent on the ability to conduct health research, the serious and growing inequalities in health research capacity between the North and the South do not bode well for the future (WHO, 1996). Nowhere is the gap in research capacity more evident or growing faster than in the genetic sciences. While genomics research has significant potential for improving the health of populations in the South, many of the leading causes of death globally have a genetic component. The current state of biotechnology expertise in the South varies widely across countries and continents. Few regions have developed biotechnology capabilities sufficient to enable them to apply future advances in genomics research to their particular public health needs. If this situation is not addressed, many populations will fail to benefit, further exacerbating inequalities in health between the North and the South (WHO, 2002). Indeed, the "10/90 Report on Health Research," which documents such disparities, suggests that strengthening research capacity is one of the most effective and sustainable ways of advancing health and development in the South (Bloom and Trach, 2001).

To promote sustainable research capacity in the genetic sciences in the South, this paper focuses on two key issues that could facilitate its development: enhancing human resources and generating financial capacity.

Relevance and Potential of Genomic Research and Technologies to the South

Areas of genomic research that are relevant to the South fall into five broad categories.

- Relatively inexpensive diagnostics for which the DNA technology has already been developed. The provision of training and technology to integrate their use into health care delivery systems can help in establishing or enhancing the technological base upon which benefits from future genetic advances can be built (WHO, 2002).
- Genetics research on vaccines and therapeutics for tuberculosis and HIV/AIDS is already progressing and has the potential to lead to long-term research collaborations and commercialized products for both diseases. This would have an immediate impact on the health of populations in both the North and the South.
- Some vaccines, therapeutics, and diagnostics are currently neglected by researchers in the North, such as leprosy, dengue, African sleeping sickness, malaria, diseases which have no market in the developed world.
- Therapeutics for non-communicable, chronic diseases such as diabetes and cancer are currently a priority in the North and increasingly important in the South. With adequate human resources, countries in the South could participate in the research as full partners.
- Pharmacogenomics: The examination of the implications of genomic variability in individual responses to drugs can certainly be enhanced by building research capacity in the South and is likely to be of interest to pharmaceutical companies worldwide in the process of research and development of new products.

The New Genetic Sciences: A Paradigm Shift

Research and training in genetic science is critical, because exploration of molecular mechanisms of disease and widespread use of genetic methodology is rapidly becoming a fundamental component of biomedical research everywhere. These new molecular tools foreshadow a paradigm shift in medicine by which we will not only prevent and treat, but also define disease (Christianson et al., 1995). The capacity to understand the consequences of these novel ways of thinking about disease risk, and what it means to have a "disease" because an individual carries a gene or a number of genes, is critical for investigators, health care providers, and for the public (Singer and Daar, 2001). Consequently, medical education is likely to undergo a fundamental shift the world over.

Since the completion of the draft sequence of the human genome, much debate has centred on more rapid and accurate diagnoses, an improved understanding of disease mechanisms, and a greater ability to predict response to drug selection. Discussion of these issues and the dialogue regarding ethical and legal issues in genetic research and genetic testing has, however, with few exceptions (Bloom and Trach, 2001; Christianson et al., 1995; Singer and Daar, 2001) focused on health and disease in the North (Collins and Guttmacher, 2001; Scheuerle, 2001).

Global Research – Global Relevance

Advances in the field of genetics, through collaborations between scientists in developed and some developing countries, have led to the physical mapping of the human genome. Additionally, international co-operation has made possible the identification of genes for cystic fibrosis, hereditary forms of colon cancer and breast cancer, hemoglobin disorders such as thalassemia, and movement disorders such as Huntington's chorea. Increasingly, as the focus moves from the relatively uncommon single gene disorders to understanding common diseases in which multiple gene interactions play a role in altering the risk for, or expression of, disease, extensive epidemiological studies will be required in different populations worldwide. These will require global collaborations, data sharing, and pooled analyses among researchers (Singer and Daar, 2001). Similarly, understanding both inter- and intra- population differences will be central to development of cost-effective medications with minimal side effects.

In addition, research conducted abroad — in both industrialized and resource-poor countries — adds to the foundation of scientific knowledge that leads to a better understanding of the establishment and progression of disease, and to the development of treatments and prevention measures that may not have been initially anticipated. For example, collaborative work in Nicaragua to develop novel, simple, and low-cost molecular diagnostic tools to detect sub-types of the dengue virus (Balmaseda et al., 1999) has been translated for use in sub-typing strains of two other serious infections: a strain of E.coli (0157H7) (a common cause of food poisoning resulting from the ingestion of undercooked hamburger) and the virus that causes hepatitis C.

New Challenges to Equity Posed by Genetic Technology

The economic and scientific context in which the development of genomic technologies takes place is, in many ways, similar to those that apply to other areas of biomedical science. These realities create difficult challenges in ensuring access to the fruits of medical research in general for populations in the South, some of which has taken place in these same populations. The development of genomic technologies thus threatens to further exacerbate global inequalities in health for several reasons.

- The process of development of genomic technologies is generally complex, laborious and expensive. Therefore, the cost of vaccines and therapeutics that result from genomic research is likely to be out of reach for much of the South.
- Since most product development in genetic sciences is performed by the private sector in industrialized countries, the primary goal of producing returns to investors will likely conflict with the goal of health equity (e.g., research may not be performed on diseases that are purely endemic to the South).
- Global health disparities will be further widened if genomics research focuses on a small but lucrative segment of the world's population, (e.g., designer therapies for small, targeted populations in the North that are developed using a pharmacogenetic approach). In contrast, this approach to product development is unlikely to be applied to populations in the South. The necessary infrastructure required to use gene-based medicines effectively (i.e., screening and diagnostics), the need to thoroughly analyze the cost effectiveness and outcomes of new interventions within particular countries and populations, and the potential change in size and complexity of clinical trials may make the cost of the research and the application of the resulting technology unaffordable for most of the South (Nuffield, 2002).
- Patents have been obtained for basic genomics research tools, including genes themselves, as well as other types of genomic information, such as expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs). The significant time and expense required to avoid infringing patents and obtain licences might discourage or delay international research. Researchers in the South are legally free to use research tools that are only patented in the North. However, where research must be done in

institutions in the North, or where researchers in the North want to use such tools in collaborative research with researchers in the South, patent limitations may become serious disincentives to performance of the research at all (Barton, 2001).

- Whether countries in the South are in the process of developing their own standards for patentability of genetic information, or whether they are negotiating licences with entities in the North for use of patented basic genomics research tools, the South will need strong capabilities in the management of intellectual property. Currently, large disparities exist globally in technology transfer capacity and intellectual property management, potentially depriving researchers in the South of needed basic research tools.
- While pockets of excellence in genetic research exist in some resource-poor settings, the numbers of people who have the expertise to perform this work in the South are few, and the research infrastructure is weak. If this growing genetic divide is to be bridged to take advantage of recent developments in genetic science and to address the diseases of poverty globally, promoting research and training programs in genetic sciences in the South is a not a luxury, but is in reality, essential. We examine why it is in the best interests of all countries to promote this capacity, what challenges lie ahead, what researchers in the South believe is needed, and how we in the North can respond.

Enhancing Genetics Research Capacity in the South

Collaborations between researchers in the North and the South offer benefits to all parties involved. The challenge is to find effective ways of boosting expertise in genetic science in the South to ensure full partnership, while avoiding the pitfall of "brain drain."

There are two major obstacles to full participation by the South: the first is financing and the second is well-qualified trained personnel. While at least $600 million was spent on genetics research by the United States government and non-profit organizations in 2000, China and Russia combined spent just $50 million. No other developing nation was able to keep pace with even this level of funding (Cook-Deegan et al., 2000). Although spending on genetics research in developing countries is dwarfed by that spent in the industrialized world, and despite the fact that the science and technology sector is seldom viewed as strategic by governments in the South (Harvard, 2001), some national governments have exhibited a strong commitment to genetic science and invested significantly in building capacity. This commitment on the part of governments in the developing world is an absolute requirement for building genomics research capacity, particularly for research that can be performed on technologies with the most local relevance for research institutions to serve as equal partners in collaborative research with each other and with the developed world.

One notable effort by a government to invest successfully in start-up funds for genetic research is that of Brazil. In 1997, scientists and policy makers in the state of Sao Paulo had the foresight to invest in efforts to sequence the genome of a phytopathogen that threatens orange and grape vineyard cultivation. The genetic information itself has been only one of the benefits, as this effort created an awareness that state-of-the-art genetic technology now exists in Brazil. As a result, funding is coming from agencies both inside the country and abroad (Rabinowicz, 2001).

As result of a three-year feasibility study, the first Mexican Center for Genomic Medicine has been established and is funded by a consortium of partners (Jimenez-Sanchez et al., 2002). These partners include the private sector in the form of the Mexican Health Foundation, the National Council for Sciences and Technology (CONACYT), the Ministry of Health, and the National Autonomous University of Mexico (UNAM), where the institute is housed. In addition to intramural research, the goal of the Center is to promote domestic and global collaborations in the public and private sectors. Interestingly, the feasibility study showed the high costs of not making this investment included a lack of competence for developing new diagnostic tools, scientific brain drain, increasing technological dependence, and fewer investment and business opportunities (Jimenez-Sanchez et al., 2002).

In 1986, the government of India established the Department of Biotechnology (DBT), which has an annual budget of approximately $30 million. The DBT is responsible for developing regulatory standards for biotechnology research in India, and its programs are implemented through research institutions and universities that receive federal grants. Through its program in human genetics and genome analysis, the DBT supports research and development activities in the genetic sciences to address local health priorities. In addition, the DBT has successfully promoted several international and regional scientific collaborations (WHO, 2002). Still other governments in the developed world have formed partnerships that successfully address financing issues. For example, the Max Planck Institutes of Germany invested in countries with a basic level of research infrastructure. In 2001, they supported the creation of a genomic centre at the National University of La Plata in Argentina, in collaboration with the association of universities of the Montevideo Group (Rabinowicz, 2001). While the experiences demonstrated by this handful of developing countries are not extensive, they do demonstrate that creative ways can be found, and more will be needed, to address funding needs (Singer and Daar, 2001; Juma, 2000).

Even less attention has been paid to the second obstacle to achieving equity — the availability of qualified researchers. To date, with the exception of pathogen genome research, a review of major funding agencies in North America and the United Kingdom revealed no targeted efforts to train researchers from the South in genetic sciences. However, a cadre of indigenous researchers who understand the science, who can negotiate with collaborators, and who can analyze the data "in country" is a prerequisite for equitable collaboration. Local research capacity will also minimize the possibility of "helicopter" research, where scientists from resource rich countries fly in, collect DNA samples and then fly out to perform the analysis. Since population-based research is unlikely to have immediate benefit for study participants, scientists will also require a clear grasp of the ethical dilemmas and potential for exploitation that could arise during the conduct of the research itself.

Based on experience with research capacity building in fields such as HIV/AIDS, medical researchers in the South frequently go on to play key roles as government policy makers and can influence health research agendas to best reflect local priorities. Leaders who emerge as a result of research and training in genetic sciences will not only be well positioned to assist their countries and regions in translating research results into innovative health care strategies, but could provide direction for developing modern health science curricula for their own institutions. Although it is not possible to entirely prevent "brain drain" (compensation and working conditions are contentious even among scientists in resource-rich countries) (O'Reilly, 1995; Williams, 2001), boosting the critical mass of trained scientists, and clinical and laboratory capacity in genetic science may help to partially stem the exodus of established and young researchers from the countries in the South that have already invested in some health research infrastructure.

NIH Research Capacity Building Efforts

The Fogarty International Center, in collaboration with NIH partner institutes and centres, has developed a program to address the research capacity gap in genetic sciences in the South. This program grew out of consultations with researchers and scientists in human genetics from the South to explore the potential infrastructure needs, the research gaps, the ethical and cultural barriers to performing genetics research and the potential risks of doing such research. It is hoped that this program will advance human genetics research globally, while enhancing the limited but growing capacity in genetic science in the South.

Consultation with scientists from the South was crucial in helping the NIH understand critical needs in the nexus between genetic technology and global public health. It is interesting to note that while these scientists endorsed the need for research on resistance and susceptibility to infectious disease and production of vaccines, they also pointed to the need to better understand the genetic contribution to chronic multiplex conditions, including cancer, heart disease, asthma and diabetes, as well as the interplay between genetic factors, the workplace, and other environmental exposures. This likely reflects the fact that although three quarters of the world's population suffers from the persistent cluster of infectious diseases and malnutrition, the World Health Organization (WHO) projected rank order of disease burden worldwide in 2020 shows a dramatic shift to chronic diseases with variable genetic contribution (Murray and Lopez, 1996), especially in urban areas in the developing world. (Unwin et al., 2001).

Scientists were also mindful of the fact that genetic research and the provision of genetic services are not conducted in isolation; use of these new technologies raises challenging questions regarding exploitation, stigmatization, ownership of genetic information, and other difficult issues that cut across many aspects of civil society. Consultation affirmed that with the advent of new genetics technology, which has the capacity to clash with culture and religion and from which there will be few, if any, immediate benefits, a greater understanding of the ethical and legal issues that arise during the process of genetic research is especially relevant for local investigators. After all, they are best suited to build trust in the communities in which they live and work. Programs that do not support parallel training in ethical, legal, and social issues as they relate to the conduct of genetic research in the South will not meet these needs.

No single program can satisfy all needs related to capacity building in genetic sciences, but the NIH have taken an initial step. In the interests of sustainability and in an effort to avoid brain drain, the NIH will, at the outset, promote collaborations and research training in settings where some genetic research capacity already exists. Complementary approaches and increased investments by other research-funding agencies will be necessary to ensure viability, expansion to other countries and, ultimately, the development of effective regional collaborations.

To promote these goals, it is also essential that institutions in the South integrate genetics into their health sciences curricula, examinations, and accreditation processes. Moreover, in the future, the changing nature of biological research will demand a multidisciplinary approach that might include teams of engineers, mathematicians, and computer programmers, so diversification of training will also be required (NIH, 2001). Without trained scientists who have both a current vision of science and understand where it is going, this cannot occur.

Conclusion

The report, *Genomics and World Health*, by the Advisory Committee on Health Research at the WHO highlights the challenges to harnessing the use of new genomic knowledge to improve health globally. It specifically focuses on the opportunities for these scientific approaches to contribute to health equity in developing countries. At the same time, it emphasizes the many reasons why it is in the interest of research funding agencies in the North and their counterparts in the South to come together to promote capacity building in the genetic sciences. Doing so is no longer an option — it is essential if we are to bridge the genetic knowledge divide toward a healthier, more equitable, and more productive world.

Table 1: Results of Consultation with Researchers from the Developing World

Infrastructure Needs:

- Train scientists in molecular biology and molecular epidemiology. Include academic researchers and physicians so the research that is done is performed in a truly collaborative fashion.
- Establish departments of genetics in medical schools.
- Public education.
- Policies and guidelines to ensure quality control of laboratory services.
- Promote dialogue on transport of tissues, cells, and DNA across national boundaries for present *and* future use and the issue of guideline enforcement.
- Address cultural concerns about obtaining access to individuals, families, cohorts, and communities.
- Monitor and evaluate the population impact of genetic tests and services.

Research Needs:

- Develop rapid, low-cost diagnostics.
- Resistance and susceptibility to infectious diseases, production of vaccines.
- Understanding mechanisms of diseases that are significant locally, including cardiovascular disease, diabetes, and cancer.
- Epidemiological analysis on the association between genetic variation and disease.
- Genetic research in the context of environmentally based risk factors – nutrition and workplace exposures to determine relative risk and to evaluate what effect these factors might have on gene expression.
- Genetic services delivery for individuals and families with single gene disorders/ birth defects.

Financial Barriers:

- Limited funds from internal and external sources, few qualified people, little government commitment to this type of research.

Ethical, Legal, and Social Barriers

- Group stigmatization.
- Disruption as a result of revealing information such as paternity.
- Misappropriation of genetic material with little benefit to the community.

References

Balmaseda, A., E. Sandoval, L. Perez, C.M. Gutierrez and E. Harris (1999) "Application of Reverse Transcriptase (RT)-PCR and Restriction Site Specific (RSS)-PCR in the 1998 Dengue Epidemic in Nicaragua," *American Journal of Tropical Medicine and Hygiene*, 61: 893-897.

Barton, J. (2001) *Patents in Genomics and Basic Research: Issues for Global Health*, Commission on Macroeconomics and Health Working Paper Series, Paper No. WG2:13, pp. 10-11.

Bloom, B. and D. Trach (2001) "Genetics and Developing Countries," *British Medical Journal*, 322: 1006-1007.

Christianson, A., G. Gericke, P. Ventner, and J. duToit (1995) "Genetics, Primary Health Care and the Third World," *South African Medical Journal*, 85: 6-7.

Collins, F.S. and A.E. Guttmacher (2001) "Genetics Moves into the Medical Mainstream," *Journal of the American Medical Association*, 286: 2322-4.

Cook-Deegan, R., C. Chan, and A. Johnson (2000) *World Survey of Funding for Genomics Research, Final Report to the Global Forum for Health Research and the World Health Organization.*

Harvard University, Kennedy School of Government (2001) Science, Technology and Innovation Program, CID, BCSIA <http://www.cid.harvard.edu/cidtech/>.

Jimenez-Sanchez, G., C. Tovar-Palacio, J.P. Laclette et al. (2002) "Development of the Institute of Genomic Medicine: A New National Institute of Health in Mexico," HGM2002 Poster Abstracts, Poster No. 307.

Juma, C. (2000) *Science, Technology and Economics Growth: Africa's Biopolicy Agenda in the 21st Century*, United Nations University, Institute for Natural Resources in Africa.

Murray, C.J.L. and A.D. Lopez (1996) *The Global Burden of Disease*, World Health Organization, Harvard School of Public Health, World Bank.

NIH (National Institutes of Health) (2001) Beyond the Beginning: The Future of Genomics, <http://www.nhgri.nih.gov/CONF/beyond01.html>.

Nuffield Council of Bioethics (2002) *The Ethics of Research Related to Healthcare in Developing Countries*, London: Nuffield Foundation, Medical Research Council, Wellcome Trust.

O'Reilly, M. (1995) "Research Institute Tries to Ease Brain Drain by Bringing Researchers Back to Canada," *Canadian Medical Association Journal*, 152: 1109-1111.

Rabinowicz, P.D. (2001) "Genomics in Latin America: Reaching the Frontiers," *Genome Research*, 11: 319-322.

Scheuerle, A. (2001) Limits of the Genetic Revolution," *Archives of Pediatric & Adolescent Medicine*, 155: 1204-1209.

Singer, P.A. and A.S. Daar (2001) "Harnessing Genomics and Biotechnology to Improve Global Health Equity," *Science*, 294: 87-89.

Unwin, N., P. Setel, S. Rashid et al. (2001) "Noncommunicable Diseases in Sub-Saharan Africa: Where Do They Feature in the Health Research Agenda," *Bulletin of the World Health Organization*, 79: 947-953.

WHO (World Health Organization), Ad Hoc Committee on Health Research Relating to Future Intervention Options (1996) *Investing in Health Research and Development*, Geneva: World Health Organization.

WHO (World Health Organization), Advisory Committee on Health Research (2002) *Genomics and World Health*, pp. 80, 94, 101.

Williams, N (2001) "Britain Counters Brain-Drain Worries," *Current Biology*, 11: R725-R726.

Part 5

Informing Government

Above and Beyond: Industry Innovation Related to Genetic Privacy

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Introduction

To date there has been little public discussion of industry innovation related to genetic privacy. Discussions on genetic privacy at conferences, in academic papers, the media and, presumably, across boardroom tables, typically focus on such things as genetic discrimination (insurance and employment), or incentives and barriers to product innovation (research and product delivery) and industrial competitiveness. Industry innovations, or lack thereof, are seldom more than a footnote.

That said, a growing number of local, national, and transnational regulatory and trade initiatives speak to genetic privacy, and there is an apparent increase in public distrust of corporate and government use and protection of personal information. This dynamic of regulation and public pressure could expose industry's current shortcomings, but it may also stimulate innovations. If these innovations are to form part of a larger framework of effective, supportable, ethical policies, then they need to be evaluated.

The purpose of this paper is to begin the process of evaluation by identifying and reviewing industry innovation related to genetic privacy. The paper opens with a review of Canada's current requirements for genetic privacy. This is followed by summaries of interviews with representatives of various corporations. These interviews focused on industry innovation related to genetic privacy and included information on apparent incentives and barriers to adopting innovations. Five practices highlighted in the interviews are then compared to a proposed benchmark to assess whether they in fact can be described as "innovative." The final section of the paper identifies areas for future research.

The reader should note that this paper is not a rigorous and exhaustive examination of industry innovation related to genetic privacy. Nor does the paper do more than touch on relevant legislation and the extensive literature on genetic privacy.[1] Such a review could not be undertaken within the available time.

For similar reasons, interviews and literature searches have been restricted in large part to the biotech sector. An examination of innovation in areas, such as the insurance sector, should form part of a more in-depth review. This paper is only where the process begins.

Genetic Privacy in Canada

> ...the use of a person's body without his consent to obtain information about him invades an area of personal privacy essential to the maintenance of his human dignity.[2]
>
> – The Supreme Court of Canada

Genetic information presents a number of unusual, if not unique, challenges to policy makers and others interested in issues of privacy. For example, the fact that one individual's genetic information may provide indirect personal information about family or even genetically linked community members raises issues about the rights of related individuals "not to know" genetic results. It also clearly creates an interest in related individuals in how genetic information is collected, used and, in particular, disclosed. This will become increasingly important as advances in genetic testing techniques make testing easier and less expensive and, consequently, more widespread. (Some information suggests that home testing kits for certain conditions are being developed in the United States and other countries and will be made available over the Internet) (Williams-Jones, 1999).

Genetic material banks also raise important issues, not least because the information that can be given up by the material is likely to increase over time. For example, material collected and used for diagnosis may be subsequently used for predictive testing or research: it is always there, available to new, as yet unknown purposes.

In 1992, the Privacy Commissioner of Canada discussed genetic privacy issues in a paper entitled *Genetic Testing and Privacy*. At that time, the most significant federal legislation relating to privacy was the *Privacy Act*.

In introducing the paper, the Privacy Commissioner stated:

> The *Privacy Act* is the focus of this report's efforts to prevent genetics from spawning another nightmare in our surveillance society. The Act, however, is simply not up to the job. It applies only to federal government institutions. Its provincial counterparts, where they exist, also apply only to government institutions under provincial jurisdiction.
>
> Even within the federal government, the Act is limited in what it can do to protect genetic privacy. One must torture its provisions almost to the breaking point to offer any meaningful privacy protection to Canadians. The *Canadian Charter of Rights and Freedoms*, medical ethics and laws on medical confidentiality offer some help. But let no one be fooled; *existing laws will not prevent realizing our worst fears about privacy abuses through genetic testing* [emphasis added].

Many technological advances have occurred since the paper's publication, not the least of which are the widespread proliferation of the Internet and the recent mapping of the human genome. The significance of these advances for genetic privacy cannot be overestimated. However, in May 2000 the Privacy Commissioner's *Annual Report* (1999-2000) stated:

> In 1992, we...recommended the government adopt legislation to ensure that genetic material was collected within a legal framework, that no one was forced to give up genetic material, that genetic testing would not be a condition of employment, and that no one would suffer discrimination for refusing to be tested. We also proposed amending the definition of personal information in the *Privacy Act* to ensure that it included both genetic samples and the information derived from their analysis.
>
> *Virtually all the recommendations have fallen on deaf ears.* With the costs for genetic tests falling, a lengthening list of conditions that tests can identify, and pressure building to develop comprehensive linked health information banks on Canadians, we still have no legal framework for this intrusive technology. We do not even know how and how much employers are using genetic testing [emphasis added].[3]

To date (spring 2002), there has been no significant change in the legislative landscape. There is a variety of privacy-related legislation in Canada that might, by implication, protect the genetic privacy of Canadians. However, with the exception of forensic DNA analysis, Canada does not identify genetic privacy as an area that requires explicit legislative protection.

Legislative Initiatives Governing Genetic Privacy in the Public Sector

Protecting personal information became increasingly important for European governments and industry in the 1980s. This drive toward data protection, spearheaded by the Organization for Economic Co-Operation and Development (OECD), had far-reaching effect.

In Canada, the *National Standards Association Model Code for the Protection of Personal Information* adopted the 10 Principles of Fair Information Practices recognized by the OECD and others as critical to the proper treatment of personal information. The 10 principles are:

1. accountability for the collection, use, or disclosure of personal information;
2. identifying purposes for which the information will be collected, used, or disclosed;
3. consent to collect, consent to use and, in particular, consent to disclose;
4. limiting collection;
5. limiting use, disclosure, and retention;
6. accuracy;
7. safeguards to control access to, use of, and integrity of information;
8. openness of protection processes, so individuals can determine how their information is handled;
9. individual access; and
10. challenging compliance.

During the 1980s and 1990s, many (not all) of these principles were incorporated into Canadian federal and provincial public sector legislation,[4] statutorily obliging the public sector to protect the privacy of individuals communicating with government. However, while the code appears fairly comprehensive, imprecise requirements and a lack of monitoring and enforcement are serious qualifications, particularly if the code was intended to provide public protection and reassurance. Industry was encouraged to adopt the Model Code, although the voluntary nature of compliance meant that industry was not bound by legislation.

Federal Legislation

While the federal *Privacy Act* governs the public sector's privacy obligations, human rights legislation (i.e., the *Canadian Human Rights Act* and its provincial counterparts) and the *Canadian Charter of Rights and Freedoms* have the potential to significantly affect privacy issues. However, none of this legislation explicitly addresses genetic privacy. In addition, differences in terminology and interpretation in human rights acts — and the fact that, from a practical standpoint, protection under the Charter is limited to situations where the federal government is implicated in violating rights and usually requires the commencement of a lawsuit — makes these somewhat cumbersome tools for protecting genetic privacy. They are further hampered by their lack of applicability to the private sector.

In contrast, the federal *DNA Identification Act* authorizes law enforcement personnel to collect, use, and disclose genetic information about individuals with respect to a specific range of criminal offences, although subsequent amendment has restricted it by clarifying a prohibition against using genetic material for anything other than forensic identification purposes. This may prevent information being used for secondary purposes, such as research unrelated to the purpose authorized by legislation. However, concerns continue to be expressed by many in the privacy and medical ethics communities over the ease with which the databases and data banks of genetic material created by this legislation — and the purposes they are put to — can be expanded.

Provincial Legislation

Many provinces have legislation similar to the federal government to control public sector use of personal information (e.g., British Columbia and Alberta both have a *Freedom of Information and Protection of Privacy Act*).[5] This control often extends down to quasi-governmental levels, including universities and other educational facilities, as well as municipal governments.

A number of provinces also have legislation recognizing an individual's right to civil action for an invasion of privacy, although the scope of protection is largely unknown. Provincial human rights legislation might offer recourse to individuals who have been discriminated against, particularly in the workplace because of actual or perceived disabilities based on genetic information. However, without specific amendments clearly designating genetic privacy as a right worth protecting, this legislation may not be interpreted to include all elements of genetic privacy.

A number of provinces are implementing or have implemented legislation protecting health information. This legislation is often designed to address the competing issues of protection of privacy and the need or desire for those in the health industry to share information without unnecessary impediments. A trend may evolve to include genetic privacy in health protection legislation as the provinces gain experience in identifying areas of concern and abuse of other health information, but to date, that has not occurred.

Legislative Initiatives Governing Genetic Privacy in the Private Sector

Much of the concern over privacy rights originally related to government's ability to gather and (potentially) misuse personal information. However, advances in technology have created a situation where businesses now have similar (or even enhanced) capabilities and can accumulate massive amounts of personal information on customers, competitors, and employees. This shift in capabilities has led many countries to recognize the necessity of imposing privacy obligations on private sector organizations. In Canada, such recognition must inevitably confront the limitations that the federal–provincial division of powers places on legislation.

For example, the purpose of the *Personal Information Protection and Electronic Documents Act* (PIPEDA) is to recognize:

> ...the right of privacy of individuals with respect to their personal information and the need of organizations to collect, use or disclose personal information for purposes that a reasonable person would consider appropriate in the circumstances.

The Act, which does not specifically refer to genetic information, incorporates by reference the 10 principles of the Model Code with only minor amendments.

PIPEDA immediately applied to any organization that discloses personal information (e.g., personal health information, including genetic information) across a provincial or national border for money or other consideration. It was applied to the commercial activities of federal works, undertakings or businesses as of January 1, 2001; personal health information was exempted until January 1, 2002. As of January 1, 2004, the Act will apply to all commercial activity by Canadian organizations unless the province in which the activity takes place has passed substantially similar legislation. However, federal power is limited to jurisdiction over trade and commerce. At no time will the Act apply to non-commercial activity or to employees, other than those in federal works, undertakings or businesses. This means that the vast majority of employees in most industries will not be protected unless and until the provinces — which have jurisdiction over non-federal employment issues — pass substantially similar legislation. While the federal government has encouraged the provinces to implement this type of legislation, only Quebec has done so. In fact, Quebec was the first jurisdiction in North America to pass personal information protection legislation protecting against its misuse by both government and the private sector.

Genetic Privacy Protection in Other Jurisdictions

Numerous states in the United States now have explicit legislation covering the collection, use, and disclosure of health information, including genetic information. These statutes generally prohibit using health information for insurance purposes, or in employment matters, except in rare, specified situations.

Federally, President Clinton signed into law a statute prohibiting discrimination in the federal workplace based on genetic testing, and in early 2001, President Bush allowed the Privacy Rule of the *Health Insurance Portability and Accountability Act* (1996) (HIPAA) to come into effect. The rule is an attempt to fill the gaps left by the patchwork of state laws designed to protect personal health information for billing and administration purposes. As such, it initially appeared to have little to do with biotechnology. However, this will change as HIPAA becomes the standard protocol for hospitals. Any company classified as a "vendor" that "runs clinical trials, provides software, or uses genetic samples" could find itself subject to the Privacy Rule (ISPI, nd).

A number of European agreements cover collecting, using, and disclosing genetic information. For example, the 43-nation Council of Europe opened the *Convention for the Protection of Individuals with Regard to Automatic Processing of Personal Data* for signature in 1981. Importantly for the development of privacy standards in other nations, this Convention includes "restrictions on transborder flows of personal data to States where legal regulation does not provide equivalent protection." Similar restrictions can be found in *Directive 95/46/Ec of the European Parliament and of the Council on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data.*

Just as the OECD's Principles of Fair Information Practices influenced privacy legislation in the 1980s and 1990s, both the Convention and the Directive's influence on international trade and commerce will have a far-reaching effect. In the case of companies and governments wanting access to data held in Europe, self-regulation, and good intentions will not be enough.

Identifying Industry Innovations Related to Genetic Privacy

Defining "innovative": To be innovative means to produce (create, adopt, implement, etc.) something new or something that is ahead of its time. We took the second of these definitions as our criterion for identifying industry innovation related to genetic privacy. For the purposes of this paper, industry innovations are those things that show a greater concern for protecting genetic privacy than is required by the current regulatory environment.

That said, the fact that there is no systematic protection of genetic privacy in Canada — and, consequently, no agreed on regulatory bottom line — challenges any attempt to identify industry innovation in this area. There is, however, information sufficient to establish a standard against which the activities of various corporations can be viewed. This includes:

- the Supreme Court of Canada's 1988 ruling (*R.* v. *Dyment*);
- the CSA *Model Code*, based on the OECD's *Principles of Fair Information Practices*;
- the Privacy Commissioner's recommendations and supporting arguments found in *Genetic Testing and Privacy*; and
- regulatory activity in other western jurisdictions, particularly in the United States and the European Union.

Based on our understanding of these regulating influences, we believe that the following criteria describe an implied regulatory bottom line. For an industry practice to be accepted as innovative, it must exceed this standard.[10]

1. No individual's genetic material is tested, collected, stored, or distributed without the individual's informed consent.
2. Genetic information derived with informed consent is shared only as described in the consent process.
3. Genetic information that is not linked to identifying information and is derived from repositories of previously gathered materials may, under some circumstances, be used without consent, but only with the approval of an independent ethics review committee.[11]
4. Genetic information that is linked to identifying information and is derived from any source may only be shared with explicit informed consent.

Identifying Innovative Industry Practices

Due to time constraints,[12] the selection of interviewees was based on a short list of personal contacts provided by various research group members, through the client (i.e., Industry Canada) and through a review of *The Globe and Mail* (2002) list of "The 50 Best companies to work for." Members of the research group contacted 10 companies from that list recognized for the respect shown their employees, speculating that these companies might practise a similar respect in relation to policies and practices relating to research subjects and potential consumers.

This section summarizes the results of interviews between members of the research group and seven representatives from five companies.[13] Interviewers also spoke to representatives of the Biotechnology Industry Organization (BIO), representing over "1,000 companies, academic institutions and biotechnology centers" in the United States, and its Canadian counterpart, BIOTECanada.

The interviews were unstructured. Within the context of "industry innovation related to genetic privacy" interviewees were encouraged to identify and describe company practices that they felt were innovative. Wherever possible, these interviews were supplemented by a review of available company information. This information was then compared to the previously stated regulatory bottom line to identify those practices that are "above and beyond."

An exception to this process was made for a company noted for a patented innovation related to protecting genetic privacy. We were unable to organize an interview with representatives of the company; however, we did review the extensive information provided on their Web site.

We have not used company names or the names of their technology in this report. Instead, each company is identified by its position in a specific sector.

A multi-national pharmaceutical company (US head office): The company representative reported that the company banks genetic data using 256-bit encryption[11] to ensure appropriate security. Using computer-assigned numbers, a sample is coded on entry with the code key held internal to the computer. This permits data to be updated while prohibiting retrieval of identifiable information.

The encrypted database records "trios" (combinations of records representing mother, father, sibling combinations) and includes an ethno-cultural module, allowing data to be retrieved based on ethnic variables. The material banks and databanks are located in an American city and have been operating for about one year.

Requests from international researchers to access DNA/plasma/serum/tissue data are sent to a review board, which evaluates each request by applying a series of questions (e.g., can the research question be answered based on the data requested and the data available). The board, made up of medical, legal, regulatory, and ethical representatives, also considers various scenarios related to the request to decide whether the research could lead to identifying individuals (e.g., by linking with information from other databases).

When asked why this company has implemented this new security system to protect privacy, the representative explained that the ability to manage research-related information and maintain personal privacy is important to both the short- and long-term success of drug development. The representative also stated the expectation that regulatory bodies will soon require the type of high-level security and review practised by the company and noted that the company will be ready for the regulations and will not lose time retooling systems.

A multi-national pharmaceutical company (US head office): Both the clinical process manager and an employee in charge of stakeholder relations at a Canadian branch of this multinational company were interviewed. While pointing out that the company did not collect genetic material in any of its research projects, the clinical process manager explained that the company follows self-imposed and other privacy standards. The employee in charge of stakeholder relations explained that he did not see the relevance of genetic or health information privacy to attracting research and development funding, nor the relevance of ensuring that Canadian standards are consistent with international standards.

According to these representatives, the company follows requirements established by the International Conference on Harmonization.[15] The company receives all data coded by number at the site where the data are collected; the company cannot identify individuals, because they do not keep a list that links individuals and numbers. One representative also stated that the company ensures "good clinical practices," and that researchers and company employees can meet Health Canada audits.

When asked to identify innovative approaches to genetic privacy within the company, the clinical process manager explained that many companies out-source the clinical process manager function. Having the position as part of the company means that there are closer and more systematic "checks and balances" to ensure that the company and its employees are in compliance with guidelines and regulations.

A Canadian biotechnology company: The key points raised by this biotechnology company representative were that:

- there is very little regulatory direction in Canada related to using genetic information; and
- industry is not generally interested in using patient-specific information beyond validating research results and marketing.

The representative — who had worked with various people in the federal government in connection with ethics, regulatory issues, and international standards — stated that the company was interested in the "Bayer[16] model," which incorporates an arm's-length advisory body including members with diverse expertise, and might consider implementing such an advisory body. The representative was asked why the company would consider an ethics mechanism (i.e., the arm's-length advisory body) that can be expensive to initiate, as well as potentially limiting or even harmful if the company is perceived to be ignoring its advice. In response, the representative emphasized the importance of public opinion, and explained that the advisory body's advice in that area might influence the company's business model (i.e., direct-to-consumer marketing) and enhance public acceptance of its products. The representative explained that public opinion on genetically modified organisms is polarizing, and the company wanted to avoid a similar effect on genetic diagnostics. "We really are interested in the betterment of mankind."

When asked why it was easier to anticipate company acceptance of the Bayer model rather than other innovations, the representative explained that his personal and ethical values are similar to his CEO's, and that he (the representative) has a history with ethical matters and regulatory affairs, including public consultation on xenotransplantation. The representative indicated that his company can demonstrate a history of consistent concern with ethics and the public trust, which will be critical for public trust in the area of gene therapy.

A Canadian-based genetic testing company (subsidiary of a multinational corporation): This company has offered non-medical genetic testing for 11 years. During this time larger firms have twice purchased the company.

Most of the company's work centres on paternity testing, including surreptitious testing. According to the company representative, this has led to the company adopting legal constructs to avoid imposing on clients a morality that they do not share. For example, in cases where a client wants a spouse or partner's clothing tested to determine whether the clothing holds DNA from a sexual partner, the company received legal advice that it could proceed with testing provided the client accepts responsibility for the legal right of possession of the article of clothing. Clients must also certify that they understand that the results of tests may not be useful in court due to a lack of continuity of possession.

The representative stated that the company had initially refused to conduct a test in the case of a male questioning whether he was the father of a child and seeking to establish paternity without the participation of the mother. However, once again, the legal advice they received was that they could conduct the test if they could document that the client accepted responsibility and assured consent of the child's mother. The resulting consent form requires the client to place a check mark next to one of four options and sign the form. The options are that the mother is:

- deceased or "whereabouts unknown";
- incompetent;
- does not have legal custody and "has been specifically deprived by a court of his or her parental authority to give consent"; or
- consented to the use of the sample for paternity testing.

A fifth option "other paternity" was considered, but it was deleted as inappropriate.

According to the representative, privacy is also "protected" in paternity testing by a policy that prohibits using a sample from a previous paternity test for testing related to a different child without new written consent from the father. When the company was licensed as a subsidiary of an American company, US policies were adapted for the Canadian context.

According to the representative, the company has three policies related to confidentiality of records for genetic testing.

- All employees sign a statement of confidentiality.
- No records may leave the office.
- Records are retained for a minimum of five years (in fact, records have been kept since the company began).

Records must be retained and confidentiality maintained as a condition of accreditation and to preserve the possibility of independent review.[17] There have been client requests to delete all records, which were refused. The consent form explains that records cannot be destroyed and that biological samples might be used on an anonymous basis for DNA database research. However, the company will destroy biological samples, if requested, for a $150 administration fee.

When asked whether there have been cases when the company protected the identity or confidentiality of clients, the representative cited one example where a lawyer threatened to subpoena a paternity test. Apparently, the company stated that they would resist the subpoena because protecting its commitment to client confidentiality was important.

The representative stated that it appears that technology is far ahead of both public concerns and regulations. This places the onus on companies to do their own work in the area of protecting genetic privacy. By way of example, the representative explained that the company is interested in providing for-profit private access to genetic tests for medical conditions outside of the health care system. This has led the company into discussions with local testing programs (i.e., the Hereditary Cancer Program, the Department of Medical Genetics) to determine the appropriate standard of care in relationship to testing and counselling. The company's conclusion is that, though counselling is not required legally, it would only provide testing with genetic counselling, because that is the clinical standard of practice.

A Canadian laboratory services company: Although this company is not involved in much primary research, they do use client/patient information in method development, but only with patient permission or anonymously.

Regardless, this laboratory services company has a privacy officer (a physician), who, along with other (unrelated) duties, is in charge of privacy and confidentiality. The position of privacy officer was created, in part, by the efforts of the current officer, who insisted that the area be developed within the company.

According to company representatives (both the senior executive and the privacy officer were interviewed), the first innovative activity was to change the views of staff and physicians to recognize that clients/patients, not the company, own both the information held by the company and control of test results. The next activity was to craft principles sufficiently robust that they do not need to be revised for each case.

The privacy officer led the development of the company-wide Privacy Policy. According to the representatives, even though it is not required of a private company, this policy is consistent with PIPEDA and the relevant *Freedom of Information and Protection of Privacy Act*. Following implementation of the policy, the company refused a request from the Center for Disease Control for access to the results of hepatitis tests, offering instead to work with the Center to develop appropriate consent protocols and then seek consent from the clients/patients.

The privacy officer explained that law lags behind good ethics: if a company bases its policies on good ethics, it can avoid continually changing its policies to keep up with the law as it adjusts to new developments. The officer also noted that data that has been "de-identified" is covered by PIPEDA, but the Act is not explicit about its use in research. Currently, genetic information is not managed differently from other laboratory information, and genetic information is sometimes the result of non-DNA tests.

A privately owned American data and genetic banking company: Although we were unable to conduct interviews with this company,[11] we feel it is important to include information that we identified through an Internet search. The company, which lists venture firms, medical research centres, pharmaceutical companies, and information technology providers as partners, states that:

> In order to develop personalized medicines, secure systems for genetic research and clinical practice are needed to assure privacy, confidentiality, and education of patients and providers.[12]

According to its Web site, the company has developed a genetic bank called "enTrust." A key part of the bank appears to be a type of consent covering banking samples and data that is referred to as "dynamic informed consent":

> ...an innovative solution to the growing expectations of research study participants and patients — that their medical and genetic information be safeguarded against unauthorized use. The informed consent process offers the study participant an opportunity to understand the goals of the research, what he or she will be expected to do, the risks and benefits, as well as the opportunity to deliberate about their decision to participate. Because the science and technology are evolving so rapidly, it is often not possible for medical researchers to envision how a sample and its accompanying medical information may be valuable in the future. The historical practice of obtaining "blanket consent" from research subjects — **consent for unspecified future use of biological samples and data generated from clinical trials, is no longer adequate for genetic research.** The concerns with this approach include:
>
> - research subjects cannot provide truly informed consent for unspecified future research that he/she does not and will not know about; and
> - much of the value of medical and genetic information is lost if there is no way to update the information [emphasis added].[10]

The company claims that dynamic informed consent allows study participants to extend and/or restrict permission to use previously collected biological samples and medical and genetic data in follow-up and ongoing studies, as well as newly initiated research. If true — once again, time did not permit the research group to discuss this issue with company representatives — dynamic informed consent could enable continued use of well-characterized patient samples as new technologies and hypotheses are developed. This could be done while significantly reducing the time and cost of patient enrollment.[11]

Biotechnology industry associations: Interviews with representatives from BIO and BIOTECanada, the biotechnology industry associations in the United States and Canada, provided some insight into how representatives view genetic privacy.

According to BIO's vice-president of bioethics, the United States biotechnology industry is very aware of genetic privacy issues and is moving forward with protection. The vice-president also noted that:

- there is a reasonable level of public awareness of the issues; and
- he expects to see rapid growth in new companies providing services to protect genetic privacy.

A review of BIO's Web site <www.bio.org> reveals a large amount of ethics-related material, including a section of Recommendations for State Privacy Legislation. Nothing in these recommendations exceeds the implied regulatory bottom line defined above. In fact, many of the recommendations are to either limit regulation of genetic privacy, or they oppose treating genetic information differently than other health information. For example, according to the recommendations:

- ownership of medical information and samples is not an appropriate mechanism for protecting privacy. Statutes that confer ownership of medical information and samples will hinder research and potentially deprive patients of the opportunity to participate in clinical trials;
- privacy legislation should protect the current practice of storing tissue samples and medical information critical to medical research; and
- privacy legislation should not require the destruction of medical information and samples, as this is detrimental to medical research.[22]

The recommendations also argue for legislation that protects individuals from discrimination based on the use of health information as a means of reducing risks associated with privacy.

According to the summary statement of the recommendations for state privacy legislation:

> Privacy of medical information is not a new issue. But as our society acquires more information — and more ways to access it — privacy and confidentiality have become urgent issues. BIO believes that medical information, of which genetic information is an integral part, should be protected by uniform, national legislation. Privacy legislation needs to be constructed carefully and prudently to protect the privacy of individuals, while facilitating medical research that can benefit us all.[23]

BIO's emphasis on the need for uniform legislation and controlling the use of health information is reflected in the *BIO Policy Statement Regarding Genetic Privacy*.[24] The Statement warns that protecting genetic privacy poses a danger to the advance and benefits of biotechnology.

In stark contrast, the president and the chair of BIOTECanada <www.biotech.ca> stated that issues related to genetic privacy are not high profile: industry in Canada is more focused on assessing human and therapeutic cloning, as well as with issues related to protecting intellectual property. These representatives stated that BIOTECanada's primary emphasis is on public awareness, understanding, and acceptance of biotechnology. They referred the research group to a Canadian company likely to be innovative in this area, because of its collaboration on genetic testing with an American company.

Assessing Industry Innovations Related to Genetic Privacy

The interviews reported above highlight five approaches to assuring genetic privacy.

- Delegated consent: assigning the consumer the responsibility to receive appropriate consent from the relevant individuals.
- Genetic counselling: using a clinical standard of practice of providing genetic counselling and releasing results to a health care professional to facilitate genetic counselling.
- Ethics boards or advisory committees: establishing a body to identify issues and review requests for access to data and DNA banks.
- System prohibition of access to identifiable information: implementing computer systems that use the Advanced Encryption Standard to track data and samples.
- Dynamic informed consent: implementing systems that permit individuals to provide or refuse informed consent for each new research project involving their personal genetic information.

With the exception of **delegated consent**, all of these approaches to assuring genetic privacy appear to exceed the implied standard for regulating genetic privacy in private industry. Delegated consent actually appears to be little more than an attempt to avoid respecting the genetic privacy of those who are being tested. While there are some instances where consent might not be required for genetic testing (e.g., in the area of forensic testing), testing for paternity or sexual infidelity does not seem to qualify for that exemption.

Genetic counselling is based on the perception that genetic testing provides complex, difficult to interpret information that often has the potential for psycho-social consequences. Understanding the social risks related to genetic testing and privacy is an important part of counselling and informed consent to testing. Providing support for comprehending genetic information and making decisions related to genetic testing is not ethically distinct from insisting on informed consent to genetic testing. In fact, it is arguable that the clinical standard of care for genetic testing requires pretest genetic counselling, and the disclosure of results by a person competent to interpret the test and its implications, and counsel clients/patients about psycho-social consequences.

However, while individuals have a right to know the result of testing done on either a direct to consumer health service basis or through a health professional, gathering and providing health information does not typically include or require counselling. This suggests that the requirement that genetic testing include informed consent does not necessarily imply a requirement to include genetic counselling. Even if genetic information is viewed as sufficiently different from health information that it requires counselling to support informed consent, it is unclear whether counselling is required by current standards, or whether providing counselling is an innovation. That said, both companies that identified genetic counselling were declaring only an *intent* to provide counselling, describing it as an activity they would undertake if they begin to provide health-related genetic testing.

Ethics boards or advisory committees are certainly not required by the implied regulatory bottom line. One reason is because of the potential conflict of interest established when industry directly funds ethics advisors whose recommendations may restrict profit-generating activities or increase costs. American institutional review boards and Canadian research ethics boards are expected to evaluate and approve research independent and isolated from commercial and scientific agendas. Industry-sponsored ethics boards or advisories may not have this critical distance or authority, and consequently are not alternatives to institutional review and research ethics boards.

That said, industry-based ethics boards might provide a level of scrutiny that could enhance privacy protection and encourage responsiveness to public or consumer concerns. If the industry accepts that some use of information is inappropriate, then using an ethics board to assess each use of information from a database might be effective.

Systems prohibition to assure that data are retrievable only in aggregate or by code number is above and beyond the current regulatory bottom line. Our discussions with industry suggested that the regulatory requirement may be advancing, and increasing levels of encryption might be required. Nevertheless, this seems an appropriate and, perhaps, efficient protection of privacy.

Dynamic informed consent, which appears to make practical, and therefore reasonable, consent from individuals to the use of their data in each new research project — whether with identifiers, anonymously, or in aggregate — is clearly above and beyond the implied regulatory bottom line. Although we were unable to pursue the topic with company representatives, it appears that the concept could be expanded to enable individuals, families, and community to maintain control over genetic information while providing access under very specific terms for mutual benefit. This could be a significant step toward the goal of earning the trust and respect of patients, families, and communities.

Incentives and Barriers to Protecting Genetic Privacy

An important part of this project was noting the specific incentives and barriers to adopting innovations to protect genetic privacy identified by the interviewees.[25] However, not all interviewees identified either incentives or barriers, variously describing genetic privacy as unimportant or as not a significant concern to industry, particularly in comparison to choices around cloning and other issues.

Barriers to Innovation

Non-uniformity of requirements:

- companies have given up running some clinical trials that included genomic or genetic testing, because the variety of provincial laws and the lack of a clear national standard make the process of receiving approvals and consents too burdensome;
- time delays are, in some cases, the result of research ethics boards not being well informed about appropriate standards; and
- the lack of clear standards for research review and genetic privacy discourage industry from trying to work with Canadian researchers and institutions.

Costs of innovation:

- electronic systems design is costly; and
- staff time, whether for a privacy officer or for several employees to serve on an ethics board or advisory, is costly.

Incentives for Innovation

Sustaining a business:

- the duty to turn a profit for shareholders implies a duty to remain in business for the long run and the perceptions that a company's technologies or practices are unethical could affect its reputation, possibly increasing its legal and financial risk and threatening its future;
- innovation related to genetic privacy may reflect a corporate responsibility that:
    - investors may recognize as reducing corporate risk; or
    - may attract investors interested in "ethical investments."

Cost avoidance:

- anticipating and preparing for the greater protection of genetic privacy in the future, avoids costs associated with retooling to meet new regulatory demands; and
- establishing appropriate mechanisms for protecting privacy is an important part of risk management and can reduce the likelihood of suits.

Ease of approval:

- demonstrating that practices and research are equal to, or better than current or proposed standards saves time;
- clear, consistent policies reduce the time required for deliberation on each request for access to data, thereby improving efficiency; and
- self-regulation may prevent over-regulation by authorities.

Trust:

- companies can gain the trust of regulators and the public by demonstrating that they are able to self-regulate.

Discussion

Most ethical, regulatory, and legal discussions of genetic privacy focus on the practice of informed consent to use personal information, the potential benefits that arise from access to such information, and institutional reform to prevent genetic information from being used in discriminatory ways.[26] However, what is characterized as "benefits" and "harms" — and whether the net effect of using information is a benefit or a harm — is controversial, resting on an individual determination of whether there are sufficient benefits from an action or activity to justify accepting potential risks.

While recognizing that genetic privacy is not an area of pressing concern to industry, it does appear that comments about genetic privacy by industry representatives — as well as many scientists and other commentators — tend to focus on issues of property and public good. These comments usually cast those who would restrict access to personal genetic information as restricting the benefits that can result from less restrictive regimes.

All of the industry informants interviewed for this paper appear to consider genetic information as part of health information and describe concerns over genetic privacy as stemming primarily from the potentially discriminatory effects of unauthorized access to health information. In addition, the literature reviewed — as well as the interviews — suggest that some regulators and industry representatives do not believe genetic information is sufficiently unique to justify treating it independent of health information. Industry emphasizes balancing this control of personal information with using the information and materials to develop and commercialize knowledge and technology, ultimately tying innovations related to genetic privacy to the development of proprietary interests.

However, the limits imposed by individual informed consent do not cover all concerns. For example, the use of informed consent as a device to protect individuals from discrimination is clearly inadequate when viewed in the context of the possible stigmatization of a community (e.g., an Aboriginal or Jewish community[27]) resulting from individual community members participating in research (Weijer et al., 1999; Weijer, 1999; Burgess and Brunger, 2000; Foster and Berensten, 1998; Burgess, 2001).

From the outset, we intentionally framed this project with a definition of genetic information that was not restricted to personal information. This allowed us to discuss with interviewees how "community information" might affect genetic privacy; however, none of the industry innovation identified in this project addresses genetic privacy in this community sense. This is not to say that work is not being done in this area — research regulators, disease-based associations, and tribal councils are among the groups evaluating innovations to address this level of genetic privacy (Weijer et al., 1999; Weijer, 1999; Maccaulay, et al., 1998) — just that there was scant evidence of that work among these companies developing and using genetic information.

There is evidence of growing concern and resistance in certain communities to participating in genetic research, because of perceived misuse of material and information. Recently UNESCO, the Canadian Institute of Health Research's Institute for Aboriginal People's Health, and the Canadian National Council for the Ethics of Health Research sponsored discussions of tribally controlled DNA banks. These discussions were the result of (among other things) the unauthorized use of genetic materials collected from the Nuu-chah-nulth First Nation for arthritis research (Tymchuk, 2000; Kleiner, 2000).

Similar concerns can be drawn from non-human cases where Aboriginal knowledge of traditional medicines and plants is used by scientists to identify and isolate therapeutic substances. This knowledge, typically held by communities for the good of communities, has often been freely shared with researchers. However, once compounds are isolated or synthesized and patented, researchers and industry investors may have opportunities to use the material in ways thought inappropriate by the community, and to profit from the knowledge, usually with little or no compensation returning to the community.

Whether originating in ethno-botanical studies of cultural knowledge, or in the incremental development of understanding in public and private labs, the series of events that lead to patentable or marketable products typically involve both good will and public investment (Baird, 1996). If the individuals and communities expected to trust researchers, regulators, and industry do not believe that the regulated proprietary use of information is in the public interest, then they will be less inclined to permit use of personal and community genetic information.

Some Aboriginal, environmental, and agricultural activist groups and ethno-botanists seem most actively and explicitly engaged in this broader level of debate concerning proprietary interests and genetic privacy. On the other hand, industry and regulators seem to treat genetic privacy and proprietary interests as largely unrelated. Ultimately, this narrow focus may lead to demands for ever-increasing levels of scrutiny, including demands by individuals and communities to review or even withdraw their genetic materials and data. Among the innovations identified here, only dynamic informed consent identified the need for enhanced genetic privacy to establish and sustain public trust necessary for research.

According to the editor of *Nature Genetics* (2001):

> It would be disappointing if the biggest hurdles to bringing these benefits to society were not technical ones but the failure to convince the public to trust that their participation in science would be to their benefit, and the inability of scientists to work with legislators to develop clear guidelines that strike the right balance between timely promotion of research and protection of people.

The Royal Society of Canada's report on food technology (RSC, nd) also spoke to trust, suggesting "trust in those who regulate technologies is a major factor in public acceptance of these technologies" and recommending increased transparency of the scientific data and rationales for regulatory decisions.

> Lack of transparency in the current approval process leads to an inability to evaluate the scientific rigor of the assessment process, and thus compromises the confidence that society can place in the regulatory framework.

Industry innovation related to genetic privacy does exist in several places. Some of these innovations reflect the influence of international regulations or other market standards. That said, it is clear that regulatory ambiguity in Canada undermines both innovation and research, creating a climate in which Canadian and foreign companies, and operations may either exploit this country's lower standards to the potential detriment of the public interest, or avoid conducting research in Canada as a consequence of regulatory uncertainty. Here, as elsewhere, there must be improved public accountability for how business is regulated and operated if both the public and industry are to benefit.

Future Research

In the course of this project, the research group reviewed *Achieving Excellence: Investing in People, Knowledge and Opportunity*, volume one of the federal government's extensive two-volume report, *Canada's Innovation* Strategy.[29] One of the report's four key targets to be accomplished by 2010 is "moderniz[ing] our business and regulatory policies to support and recognize innovation excellence while protecting our quality of life." The report recognizes that industry activity, such as research and development, often occurs where boundaries are clearly defined: a clear, regulatory pathway means products move from concept to market more quickly. We believe that clarity and uniformity related to the practice and regulation of genetic privacy builds public trust through open, thoughtful debate, and is ultimately productive of industry activity and private investment.

With that in mind, future research in this area should be conducted taking into consideration the following points.

- Future research into industry innovation related to **genetic privacy should recognize that genetic privacy** is a component of health information privacy and avoid reductionist presumptions about the uniqueness of genetic information. Broadening the question to health information privacy and its relationship to genetic information will capture innovations that might otherwise be missed. For example, companies that state that they do not have practices related to genetic privacy (or have not begun to handle genetic information) may well have practices that apply to all health or research information, thereby including genetic information. This is particularly true given the fact that industry representatives strongly expressed the opinion that genetic information should not be handled differently than other health information.
- **Health information privacy may not fully cover concerns raised by genetic privacy.** For example, while both genetic information and epidemiological observation might characterize an identifiable community or a family as "at risk" of a higher incidence for a disease, genetic information currently has the greater cultural power to stigmatize. That said, there is a tendency to presume that if the problem is not unique to genetics, then it can be managed as it has been previously. This attitude neglects or is ignorant of the complex social and medical role of genetics and can lead to a belief that the existing rules provide adequate protection for all research. Developing insight into the moral issues of research or genetics will require reassessing and (often) redesigning moral practice, if what is simply poorly developed moral perception is not to be mistaken for well-considered and justified moral practice.

- It appears economical for industry to establish one set of practices that meet the highest standards of some jurisdictions and then use them in all jurisdictions; however, **inconsistencies between internationally relevant standards and Canadian regulations or practices may sometimes represent different assessments of responsibility.** For example, is consent required for secondary, confidential use of banked tissue by the researcher who originally collected the materials with open-ended consent? Conflicting requirements, or lack of knowledge of international standards, may lead to Canadian research ethics boards rejecting practices that exceed the required protection of genetic privacy, possibly undermining genuine industry innovation that provides enhanced protection of genetic privacy.

Proposed Research Topics

Issues of public trust populate a larger context than just the area of genetic privacy. And while there is much to learn from this larger context, the complexity of different concerns and interests tends to produce evaluations based on broad political convictions. A more limited focus on control of genetic information provides a more practical scope for collecting specific data and evaluating alternatives in an attempt to understand the relationship of public trust and the interests of science and technology.

Sustaining Industry Innovation Related to Genetic Privacy

Future Industry Canada research into industry innovation related to genetic privacy should focus on understanding how innovations are sustained within for-profit organizations.

Some of the motivations cited in this report in support of industry innovation included:

- the dedication of a single individual;
- concurrence between an individual pushing for ethical innovation and the company's CEO; and
- the pressure of particular media events or public concerns.

Although all of these may be necessary to initiate innovation, they cannot sustain it. Changes in senior management or the number of inspired employees, or in the public's focus are all likely to undermine innovations that are not linked to systemic motivations. Typically, these motivations in industry are such things as profit, cost reduction, increased market share, and avoiding litigation. Successful industry innovation related to genetic privacy — and by that we mean enduring innovations that protect privacy while meeting industry's needs — will likely be linked to one of these motivations. Due to market competitiveness, successful innovations sustained by systemic incentives are likely to proliferate.

The Proprietary Control of Information and its Relationship to the Public Good

Future Industry Canada research should identify and assess the degree to which various industry innovations and regulator mechanisms, such as patents, enhance or undermine the public's trust in regulators and proprietary regimes related to genetic privacy. The public's trust in the accountability of both regulators and industry influences individual and group definitions of "adequate protection of privacy," as well as the willingness to provide access to genetic information. Consequently, just as an understanding of control of genetic information should not be separated from a general evaluation of the control of health information, the control of genetic/health information at the regulatory and proprietary level should not be separated from a more general evaluation of regulatory and proprietary regimes.

Major theorists of justice have pointed out that there are problems in accepting the assumption that adequate representation and accountability is provided by the dominant "co-operative frameworks," that is market and democratic participation (Buchanan et al., 2000). At the same time, science and health-based sectors have undertaken public consultation that is often considered biased by the scientific faith that knowledge will always lead to benefit, independent of how that knowledge and technology is owned and distributed. Industry Canada is well placed to actually lead demonstration projects that establish where proprietary arrangements produce benefits and where they hinder them, and to engage the public in these evaluations. This research into different models for how political and ethical values can be embodied in corporate and governance activities, and how specific proprietary arrangements serve the public interest will itself increase public trust.

Research should evaluate how to emphasize responsibility and the complex environment of trust, rather than adopting the common practice of making liability the focus. Questions could include:

- Is there a means of designing inclusive processes of regulation and corporate responsibility that engages the public in shaping how genetic and other information is to be used?
- What is the range of public benefits that should be encouraged from the perspectives of industry, researchers, regulators, and a diverse public?

- What regulatory mechanisms or industry innovations inspire trust and shared responsibility for how social and corporate priorities are established?

Industry/Regulatory Partnerships: Combined Strengths and Conflicts of Interest

Future Industry Canada research should identify and assess the degree to which industry involvement with regulatory, governing, and academic bodies may affect the public's trust in those institutions. The (apparently) natural collaboration of industry and government on issues such as how best to stimulate innovation in the public interest, suggests that holding regulatory and governing bodies publicly accountable requires evaluating how well industry and government decisions and arrangements serve the public interest. Such an accounting is in industry and government's interest if they are to assure the public that regulatory and proprietary regimes serve the public interest.

Consistent with other areas in applied ethics, identifying situations of serious and systemic controversy indicates an opportunity for productive and important research. The public trust in collaborative arrangements between industry and public institutions is itself worthy of study. For instance, in the context of genetic privacy:

- Are there situations where limits on research or costly privacy protection would decrease in importance to participants if they had more participation in, and knowledge of, the governing structures?
- Will private, for-profit companies be more successful than public institutions in establishing DNA and data banks with appropriate privacy protections?
- What are the variables that influence participation?
- What are the actual effects of access to health and genetic information on benefits to the public and health?

Research establishing and tracking measures of public trust and transparency of process related to different partnerships with industry could provide important data to assess how best to match industry collaboration and investment in genetic privacy with accountability to public interests. Public–private collaboration on what contributes to social well-being and public health should provide specific guidance to an innovation agenda.

Notes

1 See CIHR (nd) and Jones (2001).

2 *R. v. Dyment* [1988] 2 SCR 417.

3 <http://www.privcom.gc.ca/information/ar/02_04_08_e.htm> at p. 14 of 116.

4 For a discussion of some of the shortcomings of such legislation as the *Privacy Act* in implementing these 10 principles, see Jones (2001).

5 Coupling privacy legislation with legislation designed to ensure accountability of government (access to information legislation) is a common Canadian feature. For example, in 2000 the pending federal legislation on personal information protection for the private sector was combined, at the last minute, with enabling legislation dealing with electronic documents, resulting in the hybrid piece of legislation known as the *Personal Information Protection and Electronic Documents Act*. Personal information protection legislation combines access to information and protection of privacy. This ambiguity is not always explicitly identified and may cloud the purpose of the legislation.

6 Generally, those activities that are interprovincial in nature, or have been specially designated as of importance to the whole of Canada (e.g., banks, airlines, telecommunications, atomic energy, interprovincial trucking, and interprovincial pipelines).

7 It also immediately governs commercial activity in the Northwest Territories, the Yukon, and Nunavut.

8 Parliament presumably does not have jurisdiction over non-commercial activity, including not-for-profit organizations such as the Canadian Institute for Health Information, which manages 14 databases, 12 containing personal or provider level data.

9 *Quebec Charter of Human Rights & Freedoms* (1975) as amended RSQ, c. C-12, s. 8; Loi modifiant la Loi sur l'accés aux documents des organismes publics et sur la protection des renseignements personnels, L.R.Q., c. A-2.1; Loi sur la protection des renseignements personnels dan le secteur privé, L.R.Q., c. P-39.

10 This "regulatory bottom line" reflects the prevailing assumptions that individuals have the authority to give consent relating to genetic information that is also about family and community. There are many peoples and cultures that do not recognize the notion of genetic privacy, and for whom the notion of genetic privacy and consent are not the relevant issues.

11 This prevailing standard reflects considerable ambiguity in all standards about whether the review should be of the bank and consent to storage of materials and data for research purposes, each use of data or materials from the bank, or both.

12 This project was effectively a five to six week project due to prolonged negotiation of the contract. Some company representatives believed that they were already participating, because two other Industry Canada-related researchers with similar projects had contacted them.

13 A further three companies were working on responses when this report came due.

14 This *Advanced Encryption Standard*, or AES, is the new US government encryption standard for computer transmission. The 256-bit encryption allows for $11\text{x}10^{77}$ different code combinations.

15 <http://www.ifpma.org/ich1.html>.

16 Bayer AG, a health care and chemicals group, is made up of approximately 350 individual companies.

17 The company's privacy policy states that employees "have access to this file area and are bound by confidentiality agreements and by professional codes of conduct as required by the technical certifying body ATTBC (Applied Technologist and Technicians of BC) and the accrediting bodies AABB (American Association of Blood Banks) and SCC (Standards Council of Canada)."

18 The company did not reply to our request for an interview within the project's brief timeframe.

19 <http://www.firstgenetic.net/ > Accessed March 17, 2002.

20 Ibid.

21 <http://www.firstgenetic.net/products_icf.html > Accessed March 17, 2002.

22 <www.bio.org/laws/state10.html>.

23 Ibid.

24 <www.bio.org/bioethics/genetic_privacy.html>.

25 The research group did not confirm the actual presence of these incentives and barriers.

26 Compare to Robertson (2001). Individual property rights are considered very briefly in Roche and Annas (2001).

27 F. Collins as cited in Wadman (1998).

28 The notion of transparency, while fundamental to democracy, is variously understood to describe a range of actions extending from a superficial informing of the public about decisions made "on their behalf," to direct public involvement in the process of determining benefits and risks, and decisions about how to govern in the public interest.

29 <http://www.innovationstrategy.gc.ca/cmb/innovation.nsf/pages/index>.

References

Baird, P.A. (1996) "Funding Medical and Health-Related Research in the Public Interest," *Canadian Medical Association Journal*, 155 (3): 299-301.

Buchanan A., D.W. Brock, N. Daniels, and D. Wikler (2000) *From Chance to Choice: Genetics and Justice*, Cambridge University Press, p. 263.

Burgess, M.M. (2001) "Beyond Consent: Ethical and Social Issues in Genetic Testing," *Nature Reviews: Genetics*, 2: 9-14.

Burgess, M.M. and F. Brunger (2000) "Collective Effects of Medical Research," in *The Governance of Health Research Involving Human Subjects*, M. McDonald, (ed.), Law Commission of Canada, pp. 141-175. <http://www.lcc.gc.ca/ en/papers/macdonald/macdonald.pdf>.

Canada, Privacy Commissioner of Canada (1992) *Genetic Testing and Privacy*, Ottawa: Minister of Supply and Services Canada. Referenced as 1992 but dated as 1995 through the Minister of Supply and Services Canada, this report is available in PDF format from the Privacy Commissioner's Web site <http://privcom.gc.ca>.

CIHR (Canadian Institutes of Health Research) (nd) *Compendium of Canadian Legislation Respecting the Protection of Personal Information in Health Research*. Information on this compendium can be found at <http://www.cihr.ca/about_cihr/ethics/compendium-e.shtml>. (It is not clear when this compendium was last updated.)

Foster. M.W., D. Berensten, and T.H. Carter (1998) "A Model Agreement for Genetic Research in Socially Identifiable Populations," *American Journal of Human Genetics*, 63: 696-702.

The Globe and Mail (2002) *Report on Business Magazine*, January <http://www.globetechnology.com/robmag/robmagi>.

ISPI (Institute for the Study of Privacy Issues) (nd) Clips 46.228: Decoding HIPAA — Are You Ready?" <http://www.PrivacyNews.com> Accessed March 14, 2002.

Jones, Derek J. (2001) *Selected Legal Issues in Genetic Testing: Guidance from Human Rights*, McGill University, 2001. This paper was originally written for the Health Canada Advisory Committee On Genetic Testing for Late Onset Diseases.

Kleiner, K. (2000) "Blood Feud," *New Scientist*, 2258 (September 30): 7.

Maccaulay, A.C. et al. (1998) "Participatory Research with Native Community of Kahnawake Creates Innovative Code of Research Ethics," *Canadian Journal of Public Health*, 89: 105-108.

Nature Genetics (2001) "Protecting Individuals and Promoting Science," editorial 28: 195-196.

Robertson, J.A. (2001) "Consent and Privacy in Pharmacogenetic Testing," *Nature Genetics*, 28: 207-209.

Roche P.A. and G.J. Annas (2001) "Protecting Genetic Privacy," *Nature Reviews: Genetics*, 2: 392-396.

RSC (Royal Society of Canada), Expert Panel on the Future of Food Biotechnology (nd) <http://www.rsc.ca/foodbiotechnology/indexEN.html>.

Tymchuk, Michael (2000) CBC Vancouver reporter whose reports ran on CBC radio on September 21 and 22, 2000.

Wadman, M. (1998) "News: Jewish Leaders Meet NIH Chiefs on Genetic Stigmatisation Fears," *Nature*, 392: 851.

Weijer, C. (1999) "Protecting Communities in Research: Philosophical and Pragmatic Challenges," *Cambridge Quarterly of Healthcare Ethics*, 8: 501-513.

Weijer, C., G. Goldsand, and E.J. Emanuel (1999) "Protecting Communities in Research: Current Guidelines and Limits of Extrapolation," *Nature Genetics*, 23: 275-280.

Williams-Jones, B. (1999) "Re-Framing the Discussion: Commercial Genetic Testing in Canada," *Health Law Journal*, 7: 49-68.

Genetics in Ontario: Mapping the Future

Anne Summers

Ontario is one of the largest provinces in Canada with a population of approximately 11 million people. As in many publicly funded jurisdictions, the Ontario government has become concerned about the potential pressures on the health care system resulting from the anticipated effect of the Human Genome Project. This effect has already become apparent in the shift in the focus in medical genetics from rare, mainly pediatric disorders to include predictive, predisposition and susceptibility testing for common adult-onset disorders (See Table 1). The Ontario Ministry of Health and Long Term Care (MOHLTC) recognized that genetic testing and eventually genetic therapies would change over time and needed to understand the scope of the problem to develop a plan to deal with it. In April 2000, the Minister announced the establishment of the Provincial Advisory Committee on New Predictive Genetic Technologies (PACNPGT). Its mandate was to develop principles, guidelines, and broad criteria to guide operational decision making regarding the introduction of new genetic technologies by the MOHLTC.

The work of the committee was divided among six subcommittees (ethical/legal, evaluation, laboratory, clinical, psychosocial, and education), which were given both general and specific tasks. The subcommittees were each given a year to meet, research, deliberate, and produce a report. Within that year, each subcommittee was asked to bring issues to the main committee for further input. In addition to the subcommittee work, the PACNPGT held a horizon-scanning day where a number of experts were invited to discuss their views on the impact of the Human Genome Project on health care. The MOHLTC also funded a public poll on attitudes of Ontario citizens to genetics in medicine.

Table 1

	Old Genetics	New Genetics
Type of tests	Mainly diagnostic	Predictive, predisposition, susceptibility
Type of disorders	Rare genetic disorders	Common disorders with a genetic component
	Predominantly pediatric	Predominantly adult-onset
	Usually a high chance of having or developing the disorder	Low to high chance of developing the disorder
Type of results	Usually, but not always, confirm or predict presence of disease but not severity	More complex risk predictions which may involve gene(s) and environmental factors

Adapted from A. Guttmacher (2001).

All the above information was combined by the PACNPGT into a final report, entitled *Genetics in Ontario: Mapping the Future*, which included 26 recommendations. This report was submitted to the Minister of Health on November 29, 2001. The terms of reference, the tasks of the subcommittees and the committee recommendations will be discussed below. The complete report is available at: <http://www.gov.on.ca/health/english/pub/ministry/geneticsrep01/genetic_report.pdf>.

Terms of Reference

In the overarching terms of reference, the MOHLTC requested advice with regard to both the short (two to three year) and long-term (10 year) impact of predictive genetic testing on the health care system. In addition, the PACNPGT was asked to develop a framework that could be used by the MOHLTC to reach future funding decisions in the area of new predictive genetic tests and treatment. The other terms of reference will be discussed in the context of subcommittee tasks. It was agreed that the PACNPGT would be informed of any federal–provincial initiatives in this area and that the work of the PACNPGT would inform the work of the federal–provincial initiative. The MOHLTC also required that the PACNPGT, to the extent possible, would include in its work a review of any similar approaches taken in other jurisdictions.

Legal and Ethical Subcommittee

This subcommittee was asked to develop mechanisms to address the legal and ethical implications of genetic predictive testing. These concerns were wide ranging and included consent, privacy, confidentiality of patient and health information, discrimination, coercion, access to care, the role of the private sector, gene patenting, patient recall, multiple tests on the same sample for the same condition and for multiple conditions, and the management of persons changing from at-risk to affected status.

Evaluation Subcommittee

Members were asked to develop an evidence-based framework for the evaluation of new genetic predictive technologies as well as a proposal for the evaluation of this framework. Part of the framework would include evaluation of benefits, risks, costs, and affordability for each new genetic test being considered for implementation. In addition, the committee was asked to formulate criteria for the ongoing evaluation of each new technology implemented.

Laboratory Subcommittee

The laboratory subcommittee was asked to examine all matters regarding laboratory predictive genetic testing. These included issues related to laboratory management, such as the assessment of the most appropriate technology for any given test, monitoring and making recommendations regarding new technological developments, development and maintenance of laboratory expertise, necessary volumes per test, criteria for selecting testing sites, appropriate turnaround times, standardized reporting, specimen repository and data management, transportation requirements for samples, and laboratory quality assurance. In addition, they were asked to look at more general concerns including licensing and insurance, regulatory requirements, gene patenting, partnerships including commercialization and the role of the private sector, and communication and privacy concerns.

Clinical Subcommittee

The work of the clinical subcommittee was to examine all issues of a clinical nature with regard to new predictive genetic technologies. The subcommittee was asked to develop eligibility criteria for testing, guidelines for offering testing to persons at risk, and recommendations regarding pre- and post-test counselling and patient follow-up. In addition, the subcommittee was asked to review regulatory requirements for persons involved in genetic testing and service standards and requirements. The subcommittee members were also asked to formulate guidelines for facilitating referrals and access to testing and related services, and for the management of persons changing from at-risk to affected status.

Psychosocial Subcommittee

The psychosocial subcommittee was asked to develop strategies for addressing the psychosocial implications of genetic screening for persons at risk and their families, and where necessary, strategies for intervention. This committee was also asked to develop recommendations for screening persons at risk who may potentially require psychosocial support and counselling, and to consider the management of persons changing from at-risk to affected status.

Education Subcommittee

The members of this subcommittee were asked to develop recommendations for public, patient, and provider education requirements as well as modalities and approaches to education, including topics such as adult education, literacy, and translation, and to review educational modalities currently available provincially, nationally, and internationally.

Recommendations of the PACNPGT

The full text of the 26 recommendations of the Advisory Committee can be found in the report. They are summarized here under 13 common areas.

Ongoing Multidisciplinary Committee

Given the far-reaching nature of the recommendations made by the PACNPGT, the first recommendation was that there be an ongoing multidisciplinary committee to oversee the process. This committee would have tasks such as horizon scanning, evaluation of new and current technologies, reviewing ethical and legal issues, making recommendations regarding human and infrastructure resources, education, developing a process for the implementation of new genetic services that includes both public and private sectors, and responding to other requests from the MOHLTC.

An Evaluation Process

The committee recommended that each new genetic service be evaluated in a timely manner by a framework, which includes legal, ethical, social, psychosocial, epidemiological, clinical, and laboratory components. This multifaceted framework has been elaborated by the evaluation subcommittee.[1] The evaluation process should involve many disciplines including consumers and, where appropriate, identified communities. The committee recognized that genetic testing may not always be the most appropriate route in the management of a particular disorder and so it was recommended that the evaluation should also balance the costs of a new genetic test against other prevention strategies. It was also felt to be very important that even where predictive testing cannot alter the course of a disease, provision of the test must still be considered, as there may be other benefits.

Programmatic Genetic Services

Genetic testing is not an isolated event. It requires an integrated, multidisciplinary service, which includes genetic assessment and counselling, quality testing, psychosocial support, and follow-up services including surveillance, prevention and treatment. Therefore, it was recommended that each new technology must be treated as a genetic service and would be evaluated on that basis. In addition, before the introduction of a new service, guidelines and care maps in the genetic management of the condition must be in place.

Education and Information

It was clear from the work of the education subcommittee, that there was a need for genetics education in all sectors of the Ontario population. Therefore, it was recommended that Ontario develop a genetics education program at all levels — for the general public, providers, educators, and patients seeking education and information about a specific disorder. It was expected that this type of program would have to involve other ministries as well as the MOHLTC.

Quality Management

Quality was also viewed in terms of the service and not the test and it was recommended that each aspect of a service be submitted to quality review. This would include pretest preparation (counselling, education materials, etc.), laboratory testing and reporting of results, post-analytical follow-up (interpretation and reporting to patients), and patient monitoring following testing. The Advisory Committee also recommended that quality be ensured for out-of-province testing.

Human Resources

The work of a number of committees showed that there was a need for increasing human resources in all areas of clinical genetics. The PACNPGT advised the MOHLTC that it address the expected impact of new genetic technologies on health services by developing strategies to encourage retention and recruitment of personnel to genetics training programs, and to introduce or enhance accredited training programs for genetic services. The Advisory Committee also recommended that the MOHLTC ensure that all personnel directly involved in genetic services work in a regulated health environment because, currently, genetic counsellors are not recognized under the *Ontario Regulated Health Professions Act*, 1991.[2]

Non-Discrimination

The Advisory Committee recommended that the *Human Rights Code*[3] be amended to prevent discrimination on the basis of genetic traits and that there be an approval system for the use of genetic testing and information in insurance, employment, etc. In addition, the Committee asked the MOHLTC to consider a moratorium on the use of genetic information by insurance companies and employers to determine eligibility for insurance or employment until such time as policies regulating use of genetic information in these contexts could be implemented.

Research

All genetic testing undertaken in the research context in Ontario will have thorough research ethics review by independent and accountable research ethics boards.

Patents, Direct Marketing and Commercialization of Tests

As patents, direct marketing, and commercialization of tests are all under federal jurisdiction, the committee recommended that the Government of Ontario engage in discussions with the Government of Canada regarding these and other areas of federal jurisdiction related to the commercial use of genetic tests.

Informed Consent

The PACNPGT felt very strongly that genetic testing always be in the context of informed consent. This consent should be express and documented indicating that discussion with the individual regarding the risks, benefits, and alternatives to the testing has taken place, as well as demonstrating the voluntary nature of the consent and the right of the individual to refuse or withdraw it.

Duty to Warn

The Advisory Committee recommended that legislation should not impose on the health care provider a duty to disclose genetic information to high-risk relatives. However, it was also recommended that the issue of physician privilege to disclose genetic information to an individual's high-risk relatives against his or her wishes, should be reviewed.

Privacy and Confidentiality

The PACNPGT recommended that within the context of privacy legislation, the MOHLTC afford special protection to genetic information particularly in the areas of privacy and control of information issuing from laboratory testing or blood and tissue samples, and the banking of newborn screening data/samples. In addition, such legislation should establish norms for the collection and storage of genetic information, for access to stored genetic data/samples, and for the standards of confidentiality regarding an individual's genetic information as related to other family members. The Committee also recommended assuring the right of a tested individual to request that his or her DNA sample be destroyed, and that genetic records be created and treated as distinct from medical records.

Genetic Testing of Minors

The PACNPGT followed international guidelines in the area of genetic testing of minors, recommending no testing where there are no timely medical or psychosocial benefits.[4] In addition, it was felt that generally, parental consent should be obtained for newborn genetic screening and that when banking newborn screening data and samples, individual rights of privacy and confidentiality should be protected, and informed consent be integral to this practice.

The work of the PACNPGT was done by a dedicated, extraordinary group of people. It is gratifying to report that our first recommendation has been implemented. On July 24, 2002, the Ontario Minister of Health and Long Term Care, the Honourable Tony Clement, announced the newly formed Provincial Advisory Committee on Genetics to be chaired by Dr. Ron Carter. It is expected that this committee will build on the work of the PACNPGT.

Acknowledgments

I would like to thank the members of the Ontario PACNPGT – Dr. Judith Allanson, Sharon Balsys, Dr. Sean Blaine (Co-Chair, Education), Dr. George Browman (Chair, Evaluation), Dr. June Carroll (Co-Chair, Education), Dr. David Cole, Dr. Colin D'Cunha, Dr. Mary Jane Esplen (Chair, Psychosocial), Dr. Alasdair Hunter (Co-Chair, Clinical), Phil Jackson, Dr. Birthe Jorgensen, Michael Kilpatrick, Trudo Lemmens (Co-Chair, Ethical/Legal), Dr. Les Levin, Dr. Alex MacKenzie, Grace Maddox, Roxanne Mykitiuk (Co-Chair, Ethical/Legal), Leela Prasaud, Dr. Kenneth Pritzker, Maureen Provencher, Francine Robert, Dr. Kirsten Rottensten, Dr. Brian Sheridan, Elaine M.W.Taylor, Adam Topp, Luke A. Vanneste, Dr. Lea Velsher (Co-Chair, Clinical), Charlotte Weiss, Dr. Philip Wyatt (Chair, Laboratory), and I would also like to thank the members of each subcommittee. This document is a review of their work.

Notes

1 <http://www.gov.on.ca/health/english/pub/ministry/geneticsrep01/genetic_report.pdf>.

2 <http://192.75.156.68/DBLaws/Statutes/English/91r18_e.htm>.

3 <http://192.75.156.68/DBLaws/Statutes/English/90h19_e.htm>.

4 The American Society of Human Genetics Board of Directors and The American College of Medical Genetics Board of Directors (1995) "Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents," *American Journal of Human Genetics*, 57: 1233-1241.

Afterword

Bartha Maria Knoppers

The integration of genetics and genomics into health care systems and public policy comes at a time when issues of health, research, and the economy are inextricably linked. Yet, there is mutual ignorance by social scientists and lab scientists of how industry really works. While different political and personal views prevail as to the role of the market, it cannot be ignored. Unbeknownst to most citizens is the time, effort, and money required to bring a product to market following the validation of research results in costly and lengthy clinical trails, to say nothing of the regulatory hurdles. Perhaps pharmacogenomics will force a greater exchange of ideas and understanding since based on access to a person's genotype, it promises individualized drugs and so the market enters the home.

The uniqueness and yet universality of genomics means we need to find the right balance between rewarding private investment in research and furthering access to knowledge for the public good. Patenting best illustrates this dialectic. As a reward for innovation and economic utility, patents play a necessary socio-economic role. Furthermore, if awarded, that know-how becomes public as opposed to a trade secret. The question then becomes one of monopolies and exclusive, (expensive?) licensing or of non-exclusive licensing with reasonable prices that allow investment to be recouped but over a longer period of time.

Universal health care systems will flounder if the genes that play a probabilistic role in common diseases are patented solely for immediate profit. Indeed, a two-tier system will result. If patentability criteria were clarified and tightened up, the issue would not be patents but rather licences and copyright subject to fair and equitable access through licensing that is in the public interest. Most important, the freedom to do non-commercial research as a legitimate exemption to patent infringement also needs to be clarified and strengthened. However, this will not avoid the increasingly pervasive conflicts of interest plaguing the university–industry alliance.

In short, there are many questions we need to think through regarding the implications of genomics for the way we organize and manage our health care system. How will this new technology be integrated into our health care system? Who is going to pay? Is this new technology likely to favour an increased share of private or public funding for health care? What mechanisms do we need to develop for evaluation and reallocation of resources among various health care options? What criteria will guide these calculations? Determining what genetic services should be covered by the public system will be a key issue for public policy. Moreover, there are substantial new challenges to equity both within and across countries. There are fiscal and moral questions about the distribution of financing for these new developments. For example, to what extent should the poor in Canada or poor countries contribute less?

Turning now to a question that comes up without fail in public discourse: "How will this information be handled in a way that protects both my privacy and that of my family?" If knowledge of genetic risk factors is to be encouraged to promote health and prevent disease, there is legitimate concern over access by employers and insurers. In Canada, with its universal health care system, employment and insurance are considered as private industries with the right to legitimately "select." Such selection has to be fair however, and based on bona fide requirements for a job or on actuarial data in insurance. Paradoxically, aside from monogenic, hereditary conditions that are relatively straightforward, it will become increasingly difficult to distinguish genetic information from medical information. It may well be this "normalization" and integration that will save us not only from stigmatization and discrimination, but also from unnecessary legislation that reinforces the notion that genetic conditions or information are different.

Legal and ethical norms are constructed on respect for the individual, while genomics is individual, familial, social, and universal. Indeed, whole populations whether homogenous or heterogeneous are of scientific interest. The need to study gene–gene and gene–environmental interactions requires longitudinal studies of populations (cohorts) over time. Whither individualistic notions of privacy? As a citizen, one cannot have the benefits of discoveries and therapies without sacrificing a portion of narrowly centred privacy.

In many ways, these technologies may alter fundamental notions of what it means to be human. They could even be destined to alter our fundamental sense of the extent to which we are free (as opposed to genetically determined). We now face the challenge that these technologies will change the boundaries of our sense of belonging or connectedness to other individuals and groups. Indeed, we will return to the understanding that "No man is an island" (J. Donne).

About the Contributors

About the Contributors

Nalini P. Anand received her B.A. from Cornell University and worked at the Institute of Medicine and coedited a report addressing policy issues in childhood vaccine development. Nalini then graduated from Stanford Law School, and went on to practise health law at Hogan & Hartson in Washington, D.C. Her areas of practice included human subjects protection regulation and medical privacy issues. Nalini now works for the Fogarty International Center and provides research and policy support to FIC on a variety of legal issues related to global health, including the use of intellectual property and licensing to promote health in the developing world.

Fredrick D. Ashbury is President, PICEPS Consultants, Inc., and holds academic appointments at McGill University and the University of Toronto. His interests include research and program evaluation studies in the areas of primary and secondary cancer prevention, patient decision making and behaviour change. He consults to government and non-governmental organizations at the national, regional, and local levels in Canada and the United States. With colleagues, he has received funding from the National Cancer Institute of Canada, Health Canada, the National Health Research and Development Program, and the Canadian Cancer Society. He actively publishes in the peer-reviewed literature.

Patricia Baird is a pediatrician, and medical geneticist, and while Head of the Department of Medical Genetics at the University of British Columbia for over a decade was extensively involved in developing services for families with genetic diseases. She has been a member of many national and international bodies, among them the National Advisory Board on Science and Technology chaired by the prime minister and the Medical Research Council of Canada, and she chaired the Federal Royal Commission on New Reproductive Technologies. She has served as an advisor to the World Health Organization in genetics in recent years, and has published extensively on the policy implications of new genetic and reproductive technologies.

Sean Blaine is Assistant Professor in the Department of Family and Community Medicine at the University of Toronto and a researcher in the Mount Sinai Hospital Family Medicine Genetics Program and the Family Healthcare Research Unit. He is a community-based family physician practising in Stratford, Ontario. Dr. Blaine has an interest in the application of genetic predictive technologies in primary care. He was recently Chair of the Health Canada Working Group on Public and Professional Educational Requirements Relating to Late Onset Disease.

John F. Barton has been a member of the Stanford Law School faculty since 1969. He has studied and consulted on international patent law for more than 20 years, working with organizations such as the Rockefeller Foundation and the World Bank, the international agricultural research community, and the trade and public goods working groups of the current Commission on Health and Development. His teaching and scholarly work, as well as participation in the current US National Research Council Committee on Intellectual Property Rights and an earlier similar committee on genetic resources, have earned him a broad technical background in patent law and its reform, particularly with regard to its role in international trade, in the balancing of intellectual property law and antitrust law, in genomics and in genetic resources.

Peter J. Bridge is Associate Professor at the departments of Medical Genetics, Pathology and Laboratory Medicine, and Medicine. He has a combination of theoretical and basic research interests associated with the molecular diagnosis of hereditary diseases. Dr. Bridge is currently working on methods of risk calculation and how to derive realistic estimates of genetic risk for counselling purposes in hereditary disorders under many different simple and complex models of inheritance. These include combinations of Mendelian and non-Mendelian inheritance, those with positive and negative family histories, those with and without DNA tests, and a number of other different parameters. These are incorporated into the second edition of his textbook, *The Calculation of Genetic Risks*, Johns Hopkins University Press, published in 1997.

Peter Bromley was formerly in the advertising industry, but left to found a consultation company that assists client companies and charitable organizations to find the values that they most cherish, to define their collective culture around those values and use them to drive their activities and products. Bromley has quantitative and qualitative models, proven in the business world, that clearly measure "constructive" and other cultures within organizations that promote or impede innovation. His recent work is on what is required to construct an innovative climate. Bromley's client contacts also helped identify innovative practices. He is one of 12 program directors for the Conference Board of Canada, responsible for the Corporate Brand/Image Conference in May.

Liam Brunham is a trainee in the University of British Columbia MD/Ph.D. program where he is completing his doctoral research in the Department of Medical Genetics under the supervision of Dr. Michael Hayden. He has won several awards for academic and research achievement, including the BC Science Council GREAT award and the Lowel Glasgow Student Research Award from the Western Society for Pediatric Research. Liam received a bachelor degree with distinction from the University of Manitoba. During his time at the U of M he founded the university's student chapter of Amnesty International and worked as science and technology editor for the student newspaper, *The Manitoban*. In addition to pursuing dual doctoral degrees, Liam is actively involved with Physicians for Global Survival, and enjoys playing the classical guitar.

Michael M. Burgess is a philosopher specializing in health care ethics. He holds the research Chair in Biomedical Ethics at the Centre for Applied Ethics, and is Professor in the Department of Medical Genetics at the University of British Columbia. His work has included qualitative research into the effects and use of genetic testing, policy related to private genetic testing and its role in the Canadian health care system, and the regulation of research to reflect diverse community perspectives. He is the lead investigator on a Genome Canada project, Democracy, Ethics and Genomics. Burgess led the team and organized the workshop in the Vancouver area.

June Carroll is an Associate Professor in the Department of Family and Community Medicine at the University of Toronto and holds the Sydney G. Frankfort Chair in Family Medicine. She practises medicine at the Mount Sinai Hospital Family Medicine Centre and is a researcher in the Mount Sinai Hospital Family Medicine Genetics Program. Dr. Carroll is interested in the integration of genetics into primary care and has several funded research projects and publications on this topic. She is also a member of several provincial and federal committees dealing with genetic service delivery.

Timothy A. Caulfield, B.Sc., LL.M., Canada Research Chair in Health Law and Policy, Associate Professor, Faculty of Law and Faculty of Medicine and Dentistry, and Research Director, Health Law Institute, University of Alberta. He has been Research Director of the Health Law Institute at the University of Alberta, since 1993. He recently received a Canada Research Chair in Health Law and Policy. He is also an Associate Professor in the Faculty of Law and the Faculty of Medicine and Dentistry. His research has focused on two general areas: genetics, ethics, and the law, and the legal implications of health care reform in Canada. Over the past several years, he has been involved in a variety of interdisciplinary research endeavours which have allowed him to publish numerous health law articles and book chapters.

Richard Gold is Associate Professor at the Faculty of Law, McGill University. He is also the BCE Chair in E-Governance. He teaches in the area of intellectual property and technology. His research centres on the nexus between technology, commerce, and ethics, particularly in the international context. In particular, he is conducting research in the area of bringing the advances of technology to the developing world. Professor Gold is Senior Advisor, Intellectual Property, to the Canadian Biotechnology Advisory Committee. He received his B.Sc. in computer science and mathematics from McGill University, his LL.B. (Hons.) from the University of Toronto, and his LL.M. and S.J.D. from the University of Michigan. He is the author of *Body Parts: Property Rights and the Ownership of Human Biological Materials* published by Georgetown University Press.

Carl B. Feldbaum is President of the Biotechnology Industry Organization (BIO) in Washington, which represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centres and related organizations in all 50 US states and 33 other nations. BIO members are involved in the research and development of health care, agricultural, industrial, and environmental biotechnology products. Mr. Feldbaum received a bachelor's degree in biology from Princeton University and his law degree from the University of Pennsylvania Law School.

John Frank trained in medicine and community medicine at the University of Toronto, in Family Medicine at McMaster University, and in epidemiology at the London School of Hygiene and Tropical Medicine. He was the founding director of research at the Institute for Work & Health in Toronto from 1991 until 1997, and is currently a senior scientist. That Institute's research program aims to identify and act upon major preventable causes of work-related disability such as low back pain.

Dr. Frank is a fellow with the Canadian Institute for Advanced Research, Population Health Program, and a full professor at the University of Toronto in the Department of Public Health Sciences. As a physician-epidemiologist, with special expertise in prevention, his main area of interest is the biopsychosocial determinants of health status at the population level. Dr. Frank was provostial advisor on population health at the University of Toronto from 1994 to 1997. From 1997 to 2001, he was adjunct professor at the School of Public Health at the University of California, Berkeley, where he recently received the Distinguished Teacher and Mentor of the Year Award. In December 2000, Dr. Frank was appointed Scientific Director of the Canadian Institutes of Health Research, Institute of Population and Public Health, located at the University of Toronto.

Michael Hayden, MB ChB PhD FRCP(C) FRSC is currently a full professor of medical genetics at the University of British Columbia, as well as Director of the Center for Molecular Medicine and Therapeutics (CMMT) in Vancouver. He has served as Chief Scientific Officer for Xenon Genetics Inc. since March 1999 and has been a member of the Board since November 1996. Author of over 400 peer-reviewed publications and invited submissions, Dr. Hayden focuses his research on genetic diseases, including genetics of lipoprotein disorders, Huntington's Disease, and predictive medicine. The recipient of numerous prestigious honors and awards, Dr. Hayden was elected to the American Society of Clinical Investigation in 1992, to the Board of the American Society of Human Genetics in 1994, and to the Royal Society of Canada in 1995. In 2001, Dr. Hayden received both the Award of Excellence of the Genetics Society of Canada, and the Ottawa Life Sciences Award of Merit. Dr. Hayden completed his medical training (1975) and received his Ph.D. in genetics (1979) from the University of Cape Town.

Karen Hofman is Director of the Division of Advanced Studies and Policy Analysis at the Fogarty International Center at the National Institutes of Health, where she is responsible for analyzing social, economic, and public health polices, and developing strategies and programs to address global health disparities through medical research. Dr. Hofman has performed clinical, molecular, and policy-related research related to pediatrics, genetics, and developmental disabilities. Prior to joining FIC, she served on the faculty at Johns Hopkins, and has consulted for the Pan American Health Organization and the Child Health Policy Unit at the University of Cape Town. She obtained her medical degree from the University of Witwatersrand in Johannesburg.

Gerald T. Keusch graduated from Harvard Medical School, and trained in internal medicine and infectious diseases. He was professor of medicine at Mt. Sinai in New York and Tufts in Boston, where he was chief of the Division of Geographic Medicine and Infectious Diseases. His research has focused on the molecular mechanisms of tropical enteric infections, AIDS, and on the interactions between nutrition, immunity, and susceptibility to infections. Since 1998, he has been Associate Director for International Research at the National Institutes of Health, and Director of its Fogarty International Center, promoting research and research capacity building in developing countries.

Brewster Kneen is a social activist and author who has organized and disseminated information related to the technological imperative. He and his wife, Kathleen, have produced *Ramshorn*, a newsletter for community-based concerns, for 21 years. He has held two grants from the Social Sciences and Humanities Research Council as an independent scholar for research in technological determinism, is author of seven books and numerous articles, and is consultant to various environmental and agricultural groups worldwide (Poland, Venezuela, California, etc.) on corporate control of agriculture and the global food system. He has degrees in economics and theology, and lives in Sorrento, BC.

Bartha Maria Knoppers, Canada Research Chair in Law and Medicine, is Professor at the Faculty of Law, Université de Montreal, Senior Researcher (C.R.D.P.) and Counsel to the firm of Borden Ladner Gervais. She is a graduate of McMaster University, (B.A.), University of Alberta (M.A.), McGill University (LL.B., B.C.L.), Cambridge University, U.K., (D.L.S.), Sorbonne (Paris I) (Ph.D.) and was admitted to the Bar of Quebec in 1985.

Currently, Chair of the International Ethics Committee of the Human Genome Organization (HUGO), she was a member of the International Bioethics Committee of the United Nations, Educational, Scientific and Cultural Organization (UNESCO) which drafted the Universal Declaration on the Human Genome and Human Rights (1993-97). She is Co-Founder of the International Institute of Research in Ethics and Biomedicine (IREB) and Co-Director of the Quebec Network of Applied Genetic Medicine (RMGA). In 1999, she became a member of the Canadian Biotechnology Advisory Committee, and in the year 2000 of the Board of Genome Canada.

Claude Laberge received his doctorate in medicine from the Université Laval à Québec in 1962. After his two-year residency in pediatrics at the Hospital for Sick Children in Toronto, he studied human genetics under Professor Victor A. McKusick at Johns Hopkins University in Baltimore, Maryland. He received his Ph.D. from Johns Hopkins in 1968. He became an associate of the Royal College of Physicians and Surgeons of Canada in 1968. He is a Professor of Pediatrics and Medicine in the Faculty of Medicine at Université Laval. From 1969 to 1993, he was director of the Réseau de médecine génétique du Québec where he was (and still is) responsible for screening newborns. Since 1993, he has been Director of the Quebec Network of Applied Genetic Medicine (RMGA) of the Fonds de recherche en santé du Québec (FRSQ). His main interests include population genetics and the transfer of genetic knowledge in the areas of public health and health policy and the lines of ethical conduct that this implies. During the last three years, with colleagues from the RMGA, he has worked to develop a strategy and research infrastructure for the Carte génétique du Québec. This map will study the distribution of genomic variations of susceptibility and polymorphism associated with environmental factors within the framework of the system of universal health care.

Graeme Laurie is Senior Lecturer in Law and Co-Director of the Arts and Humanities Research Board Centre for Studies in Intellectual Property and Technology Law at the University of Edinburgh. His research interests include the role of the law in promoting and regulating science, medicine and technology. He is author of *Genetic Privacy: A Challenge to Medico-Legal Norms* (Cambridge University Press, 2002) and co-author of *Law and Medical Ethics* (Butterworths, 2002).

Noëlle Lenoir is a diplomat to the IEP in Paris and has a DES in public right. She chaired UNESCO's International Bioethics Committee from 1992 to 1998 and, in this capacity, authored the *Universal Declaration on the Human Genome and Human Rights* which was adopted by the United Nations General Assembly in 1998. She also chaired, from 1994 to 2001, the European Ethics Group of the European Commission. She is also a Professor at the Faculty of Law of London University, Columbia University and Yale University and is an associate professor at HEC.

Patrick Lewis is an award winning writer (*Western Canada Magazine* Award: Science and Technology Writing), editor and project manager. Senior consultant and executive director to nine provincial commissions, he is a principal of ELM Group, Quality in Healthcare and an associate of Praxis Inc., a public consultation company. Specializing in interpreting and presenting complex information in health, justice, and a variety of other social policy areas, Lewis recently collaborated with Burgess in the successful design and authorship of a major application to Genome Canada entitled Democracy, Ethics and Genomics.

Margaret Lock is the Marjorie Bronfman Professor in Social Studies in Medicine in the Department of Social Studies of Medicine and the Department of Anthropology at McGill University. Prof. Lock received her Ph.D. in anthropology from the University of California, Berkeley and held a post-doctoral fellowship at the University of California, San Francisco. She has been teaching at McGill University for over 25 years in both the medical and arts faculties. Prof. Lock has served on the Culture, Health and Human Development Committee of the Social Science Research Council (US); the Medical, Ethical, Legal and Social Issues Committee of the Canadian Human Genome Project (CGAT); Health Canada's Discussion Group on Embryo Research; and a committee on ethics and organ transplantation sponsored by the World Health Organization. She is Co-Chair of the Priority and Planning Committee for Environmental, Legal, Ethical and Social Issues for the Canadian Institutes of Health Research, Institute of Genetics.

Geoffrey Lomax is the Research Director with the California Environmental Health Tracking Program. He has been conducting environmental and occupational health research since 1985. His doctoral research involved an evaluation of the scientific, ethical, legal, and policy issue related to workplace biomonitoring and genetic testing. He continues to work with the California Occupational Health Branch on ethics and health policy issues. His Dr P.H. research and M.P.H. work were performed within the Division of Environmental Health Sciences at the University of California at Berkeley and his B.S. in environmental toxicology was conferred by the University of California at Davis.

Veronica McCaffrey has experience in biomedical technology from many perspectives — in industry (including regulatory affairs, clinical trial management, and intellectual property protection and management), within the university research system, with hospitals and health care organizations, with health insurers and other payors, and with government in health products regulation. She is a lawyer focusing on health care and biomedical technology.

Kate Murashige is a partner at Morrison & Foerster and co-chair of the firm's Patent Group. Her practice focuses on the pharmaceutical and health care industries. Dr. Murashige was a member of the former National Biotechnology Policy Board for National Institutes of Health, and is a past chairperson of the Biotechnology Committee of the American Intellectual Property Law Association. She has been an invited speaker at the Human Genome Conference of patent matters and has been an advisor on gene patenting to the OTA. She has spoken before members of congress and their staffs regarding the Human Genome Project. She was chosen as one of the best lawyers in Washington by her peers.

Mark J. Poznansky, is President and Scientific Director, Robarts Research Institute, London and Professor of Biochemistry, University of Western Ontario (1993-present). From 1984 to 1993, Dr. Poznansky was associate dean of research, University of Alberta, Edmonton, where he was instrumental in the creation of several start-up biotechnology companies. Dr. Poznansky has served on the Selection Committee, Canadian Network of Centres of Excellence and Medical Research Council of Canada Grants Panel and is the holder of several patents. In his role as Director of the Robarts Research Institute, he has overseen the doubling of research activities and the establishment of seven spinoff companies in the areas of biotechnology and medical devices. He sits on the boards of several companies and numerous provincial and national research committees.

Charles Scriver is the founder of the DeBelle Laboratory in Biochemical Genetics at the Montréal Children's Hospital. His discovery of hereditary forms of rickets in children followed his lobby for the addition of vitamin D to marketed milk in Quebec. He also developed and instituted a method of examining the blood of newborn infants to screen them for a number of inherited biochemical conditions, such as PKU and hypothyroidism, allowing early and effective treatment. Scriver holds a B.A. and an M.D. from McGill University.

Lorraine E. Sheremeta joined the Health and Law Institute as a Research Associate in October 2001. She is a graduate of the University of Alberta and was called to the bar in 2001. Lori articled at Oyen Wiggs Green & Mutala, a Vancouver law firm specializing in intellectual property. She is currently working with Tim Caulfield on the Social-Political Concerns, Regulatory Policy and the Commercialization of Genomic Technologies (Genome Prairie) Project.

Calvin R. Stiller, C.M., O.Ont., M.D., F.R.C.P.(C), is Chairman and Chief Executive Officer of CMDF, CMDF II. He was co-founder and chair of Diversicare Corporation (a health care corporation) (1974-1982), and a member of the Council and Executive Committee of the Medical Research Council of Canada (1987-1993). He is a Professor of Medicine, University of Western Ontario, director of several corporations, and the recipient of numerous awards including the MEDEC Award (1992), the Order of Canada (1995) and the Order of Ontario (2000).

Anne Summers chaired the Ontario Provincial Advisory Committee on New Predictve Genetic Technologies from April 2000 to November, 2001. The Committee was charged by the Ontario Minister of Health with developing a framework for the evaluation and introduction of new genetic technologies. Dr. Summers is a pediatrician and clinical geneticist who practises in the Genetics Program at North York General Hospital in Toronto. Her particular areas of interest are prenatal diagnosis, genetic testing for adult onset disorders, and medical bioethics as it applies to genetics.

Ron Yamada is one of the founders of MDS Inc. and is the Executive Vice President, Global Markets and Corporate Affairs. His responsibilities involve identifying emerging trends in science and technology, government policies and regulations, and new market opportunities. MDS is a strong proponent of public/private sector partnerships. Ron has been involved in a wide range of organizations including HealNet, an NCE health information research network, and the Centre for Health Evaluation and Policy Analysis (CHEPA) of McMaster University. He serves as a member of the board of the Change Foundation, the Board of Governors of the University of Western Ontario, and the Ontario Science and Innovation Council.